



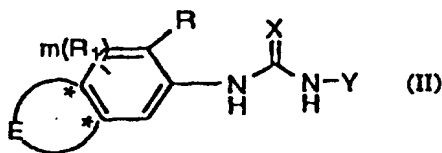
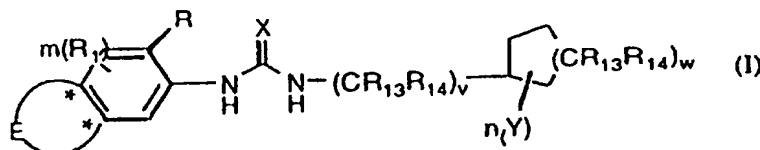
PCT

WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification ⁶ : C07C 335/00, 273/00		A1	(11) International Publication Number: WO 97/49680
			(43) International Publication Date: 31 December 1997 (31.12.97)
(21) International Application Number: PCT/US97/10903 (22) International Filing Date: 24 June 1997 (24.06.97) (30) Priority Data: 60/021,973 27 June 1996 (27.06.96) US 60/020,658 27 June 1996 (27.06.96) US (71) Applicant (for all designated States except US): SMITHKLINE BEECHAM CORPORATION [US/US]; One Franklin Plaza, Philadelphia, PA 19103 (US). (72) Inventor; and (75) Inventor/Applicant (for US only): WIDDOWSON, Katherine, L. [CA/US]; 1047 Old Valley Forge Road, King of Prussia, PA 19406 (US). (74) Agents: DINNER, Dara, L. et al.; SmithKline Beecham Corporation, Corporate Intellectual Property, UW2220, 709 Swedeland Road, P.O. Box 1539, King of Prussia, PA 19406-0939 (US).			(81) Designated States: AL, AM, AU, BB, BG, BR, CA, CN, CZ, EE, GE, GH, HU, IL, IS, JP, KG, KP, KR, LK, LR, LT, LV, MD, MG, MK, MN, MX, NO, NZ, PL, RO, SG, SI, SK, TR, TT, UA, US, UZ, VN, YU, ARIPO patent (GH, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG). Published With international search report. Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.

(54) Title: IL-8 RECEPTOR ANTAGONISTS



(57) Abstract

This invention relates to the use of phenyl ureas of formulas (I) and (II) in the treatment of disease states mediated by the chemokine, Interleukin-8 (IL-8). The variables of (I) and (II) are defined herein.

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AL	Albania	ES	Spain	LS	Lesotho	SI	Slovenia
AM	Armenia	FI	Finland	LT	Lithuania	SK	Slovakia
AT	Austria	FR	France	LU	Luxembourg	SN	Senegal
AU	Australia	GA	Gabon	LV	Latvia	SZ	Swaziland
AZ	Azerbaijan	GB	United Kingdom	MC	Monaco	TD	Chad
BA	Bosnia and Herzegovina	GE	Georgia	MD	Republic of Moldova	TG	Togo
BB	Barbados	GH	Ghana	MG	Madagascar	TJ	Tajikistan
BE	Belgium	GN	Guinea	MK	The former Yugoslav Republic of Macedonia	TM	Turkmenistan
BF	Burkina Faso	GR	Greece			TR	Turkey
BG	Bulgaria	HU	Hungary	ML	Mali	TT	Trinidad and Tobago
BJ	Benin	IE	Ireland	MN	Mongolia	UA	Ukraine
BR	Brazil	IL	Israel	MR	Mauritania	UG	Uganda
BY	Belarus	IS	Iceland	MW	Malawi	US	United States of America
CA	Canada	IT	Italy	MX	Mexico	UZ	Uzbekistan
CF	Central African Republic	JP	Japan	NE	Niger	VN	Viet Nam
CG	Congo	KE	Kenya	NL	Netherlands	YU	Yugoslavia
CH	Switzerland	KG	Kyrgyzstan	NO	Norway	ZW	Zimbabwe
CI	Côte d'Ivoire	KP	Democratic People's Republic of Korea	NZ	New Zealand		
CM	Cameroon	KR	Republic of Korea	PL	Poland		
CN	China	KZ	Kazakhstan	PT	Portugal		
CU	Cuba	LC	Saint Lucia	RO	Romania		
CZ	Czech Republic	LI	Liechtenstein	RU	Russian Federation		
DE	Germany	LK	Sri Lanka	SD	Sudan		
DK	Denmark	LR	Liberia	SE	Sweden		
EE	Estonia			SG	Singapore		

IL-8 RECEPTOR ANTAGONISTS

5

FIELD OF THE INVENTION

This invention relates to a novel group of phenyl urea compounds, processes for the preparation thereof, the use thereof in treating IL-8, GRO α , GRO β , GRO γ , NAP-2 and ENA-78 mediated diseases and pharmaceutical compositions for use in such therapy.

10

BACKGROUND OF THE INVENTION

Many different names have been applied to Interleukin-8 (IL-8), such as neutrophil attractant/activation protein-1 (NAP-1), monocyte derived neutrophil chemotactic factor (MDNCF), neutrophil activating factor (NAF), and T-cell lymphocyte chemotactic factor. Interleukin-8 is a chemoattractant for neutrophils, basophils, and a subset of T-cells. It is produced by a majority of nucleated cells including macrophages, fibroblasts, endothelial and epithelial cells exposed to TNF, IL-1 α , IL-1 β or LPS, and by neutrophils themselves when exposed to LPS or chemotactic factors such as FMLP. M. Baggiolini et al, J. Clin. Invest. 84, 1045 (1989); J. Schroder et al, J. Immunol. 139, 3474 (1987) and J. Immunol. 144, 2223 (1990); Strieter, et al, Science 243, 1467 (1989) and J. Biol. Chem. 264, 10621 (1989); Cassatella et al, J. Immunol. 148, 3216 (1992).

15

20

GRO α , GRO β , GRO γ and NAP-2 also belong to the chemokine a family. Like IL-8 these chemokines have also been referred to by different names. For instance GRO α , GRO β , and GRO γ have been referred to as MGS α , β and γ respectively (Melanoma Growth Stimulating Activity), see Richmond et al, J. Cell Physiology 129, 375 (1986) and Chang et al, J. Immunol. 148, 451 (1992). All of the chemokines of the a-family which possess the ELR motif directly preceding the CXC motif bind to the IL-8 B receptor.

25

30

treating IL-8, GRO α , GRO β , GRO γ , NAP-2 and ENA-78 stimulate a number of functions in vitro. They have all been shown to have chemoattractant properties for neutrophils, while IL-8 and GRO α have demonstrated T-lymphocytes, and basophiles chemotactic activity. In addition IL-8 can induce histamine release from basophils from both normal and atopic individuals GRO- α and IL-8 can in addition, induce lysosomal enzyme release and respiratory burst from neutrophils.

35

IL-8 has also been shown to increase the surface expression of Mac-1 (CD11b/CD18) on neutrophils without de novo protein synthesis. This may contribute to increased adhesion of the neutrophils to vascular endothelial cells. Many known diseases are characterized by massive neutrophil infiltration. As IL-8, Gro α , GRO β , GRO γ and NAP-2 promote the accumulation and activation of neutrophils, these chemokines have been implicated in a wide range of acute and chronic inflammatory disorders including psoriasis and rheumatoid arthritis, Baggiolini et al, FEBS Lett. **307**, 97 (1992); Miller et al, Crit. Rev. Immunol. **12**, 17 (1992); Oppenheim et al, Annu. Rev. Immunol. **9**, 617 (1991); Seitz et al., J. Clin. Invest. **87**, 463 (1991); Miller et al., Am. Rev. Respir. Dis. **146**, 427 (1992); Donnelly et al., Lancet **341**, 643 (1993). In addition the ELR chemokines (those containing the amino acids ELR motif just prior to the CXC motif) have also been implicated in angiostasis. Strieter et al, Science **258**, 1798 (1992).

In vitro, IL-8, Gro α , GRO β , GRO γ and NAP-2 induce neutrophil shape change, chemotaxis, granule release, and respiratory burst, by binding to and activating receptors of the seven-transmembrane, G-protein-linked family, in particular by binding to IL-8 receptors, most notably the B-receptor. Thomas et al., J. Biol. Chem. **266**, 14839 (1991); and Holmes et al., Science **253**, 1278 (1991). The development of non-peptide small molecule antagonists for members of this receptor family has precedent. For a review see R. Freidinger in: Progress in Drug Research, Vol. 40, pp. 33-98, Birkhauser Verlag, Basel 1993. Hence, the IL-8 receptor represents a promising target for the development of novel anti-inflammatory agents.

Two high affinity human IL-8 receptors (77% homology) have been characterized: IL-8Ra, which binds only IL-8 with high affinity, and IL-8Rb, which has high affinity for IL-8 as well as for Gro α , GRO β , GRO γ and NAP-2. See Holmes et al., supra; Murphy et al., Science **253**, 1280 (1991); Lee et al., J. Biol. Chem. **267**, 16283 (1992); LaRosa et al., J. Biol. Chem. **267**, 25402 (1992); and Gayle et al., J. Biol. Chem. **268**, 7283 (1993).

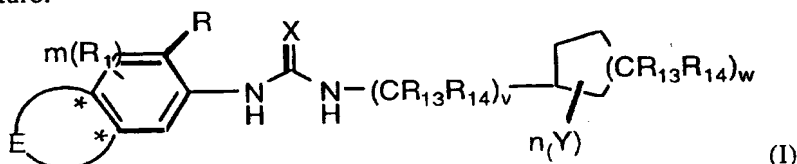
There remains a need for treatment, in this field, for compounds which are capable of binding to the IL-8 a or b receptor. Therefore, conditions associated with an increase in IL-8 production (which is responsible for chemotaxis of neutrophil and T-cells subsets into the inflammatory site) would benefit by compounds which are inhibitors of IL-8 receptor binding.

SUMMARY OF THE INVENTION

This invention provides for a method of treating a chemokine mediated disease, wherein the chemokine is one which binds to an IL-8 a or b receptor and which method comprises administering an effective amount of a compound of Formula (I) or (II) or a pharmaceutically acceptable salt thereof. In particular the chemokine is IL-8.

This invention also relates to a method of inhibiting the binding of IL-8 to its receptors in a mammal in need thereof which comprises administering to said mammal an effective amount of a compound of Formula (I) or (II).

Compounds of Formula (I) useful in the present invention are represented by the structure:



wherein

X is oxygen or sulfur;

R is any functional moiety having an ionizable hydrogen and a pKa of 10 or less;

R₁ is independently selected from hydrogen; halogen; nitro; cyano; halosubstituted C₁-10 alkyl; C₁-10 alkyl; C₂-10 alkenyl; C₁-10 alkoxy; halosubstituted C₁-10 alkoxy; azide; (CR₈R₈)_q S(O)_tR₄; hydroxy; hydroxy C₁-4alkyl; aryl; aryl C₁-4 alkyl; aryloxy; aryl C₁-4 alkyloxy; heteroaryl; heteroarylalkyl; heterocyclic, heterocyclic C₁-4alkyl; heteroaryl C₁-4 alkyloxy; aryl C₂-10 alkenyl; heteroaryl C₂-10 alkenyl; heterocyclic C₂-10 alkenyl; (CR₈R₈)_qNR₄R₅; C₂-10 alkenyl C(O)NR₄R₅; (CR₈R₈)_q C(O)NR₄R₅; (CR₈R₈)_q C(O)NR₄R₁₀; S(O)₃H; S(O)₃R₈; (CR₈R₈)_q C(O)R₁₁; C₂-10 alkenyl C(O)R₁₁; C₂-10 alkenyl C(O)OR₁₁(CR₈R₈)_q C(O)OR₁₂; (CR₈R₈)_q OC(O) R₁₁; (CR₈R₈)_qNR₄C(O)R₁₁, (CR₈R₈)_q NHS(O)₂R₁₇, (CR₈R₈)_q S(O)₂NR₄R₅; or two R₁ moieties together may form O-(CH₂)_sO- or a 5 to 6 membered unsaturated ring;

n is an integer having a value of 1 to 3;

m is an integer having a value of 1 to 3;

q is 0, or an integer having a value of 1 to 10;

s is an integer having a value of 1 to 3;

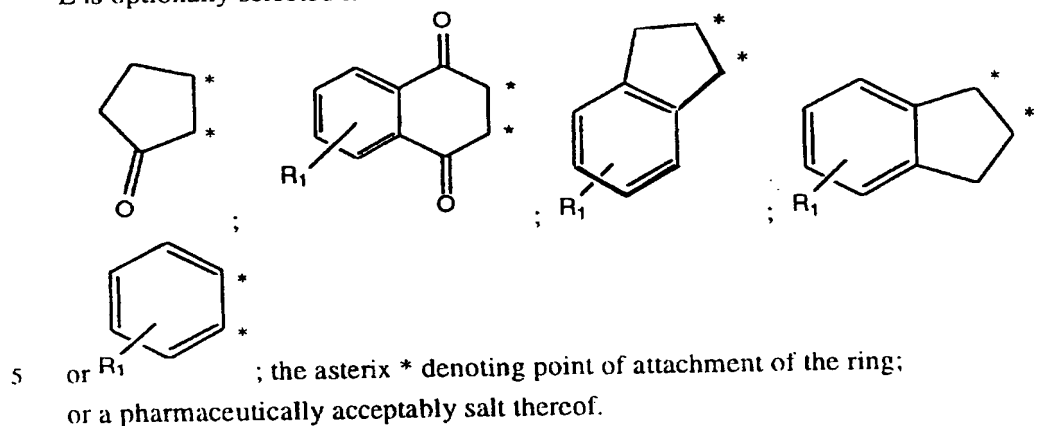
t is 0, or an integer having a value of 1 or 2;

v is 0, or an integer having a value of 1 to 4;

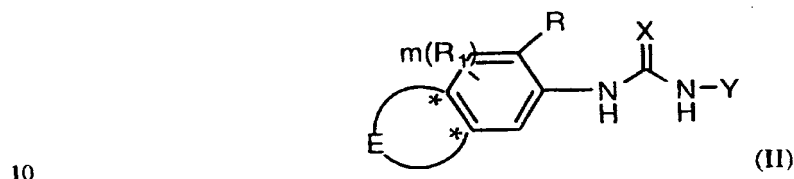
- w is an integer having a value of 1 to 3;
- R₄ and R₅ are independently hydrogen, optionally substituted C₁₋₄ alkyl, optionally substituted aryl, optionally substituted aryl C₁₋₄alkyl, optionally substituted heteroaryl, optionally substituted heteroaryl C₁₋₄alkyl, heterocyclic, heterocyclic C₁₋₄ alkyl, or R₄ and R₅ together with the nitrogen to which they are attached form a 5 to 7 member ring which may optionally comprise an additional heteroatom selected from oxygen, nitrogen, or sulfur;
- Y is independently selected from hydrogen; halogen; nitro; cyano; halosubstituted C₁₋₁₀ alkyl; C₁₋₁₀ alkyl; C₂₋₁₀ alkenyl; C₁₋₁₀ alkoxy; halosubstituted C₁₋₁₀ alkoxy; azide; (CR₈R₈)_q S(O)_tR₄; hydroxy; hydroxyC₁₋₄alkyl; aryl; aryl C₁₋₄ alkyl; aryloxy; arylC₁₋₄ alkyloxy; heteroaryl; heteroarylalkyl; heteroaryl C₁₋₄ alkyloxy; heterocyclic, heterocyclic C₁₋₄alkyl; aryl C₂₋₁₀ alkenyl; heteroaryl C₂₋₁₀ alkenyl; heterocyclic C₂₋₁₀ alkenyl; (CR₈R₈)_q NR₄R₅; C₂₋₁₀ alkenyl C(O)NR₄R₅; (CR₈R₈)_q C(O)NR₄R₅; (CR₈R₈)_q C(O)NR₄R₁₀; S(O)₃H; S(O)₃R₈; (CR₈R₈)_q C(O)R₁₁; C₂₋₁₀ alkenyl C(O)R₁₁; C₂₋₁₀ alkenyl C(O)OR₁₁; C(O)R₁₁; (CR₈R₈)_q C(O)OR₁₂; (CR₈R₈)_q OC(O) R₁₁; (CR₈R₈)_q NR₄C(O)R₁₁, (CR₈R₈)_q NHS(O)₂R_d, (CR₈R₈)_q S(O)₂NR₄R₅; or two Y moieties together may form O-(CH₂)_sO- or a 5 to 6 membered unsaturated ring;
- R₆ and R₇ are independently hydrogen or a C₁₋₄ alkyl group, or R₆ and R₇ together with the nitrogen to which they are attached form a 5 to 7 member ring which ring may optionally contain an additional heteroatom which heteroatom is selected from oxygen, nitrogen or sulfur;
- R₈ is independently selected from hydrogen or C₁₋₄ alkyl;
- R₁₀ is C₁₋₁₀ alkyl C(O)₂R₈;
- R₁₁ is hydrogen, C₁₋₄ alkyl, optionally substituted aryl, optionally substituted aryl C₁₋₄alkyl, optionally substituted heteroaryl, optionally substituted heteroarylC₁₋₄alkyl, optionally substituted heterocyclic, or optionally substituted heterocyclicC₁₋₄alkyl;
- R₁₂ is hydrogen, C₁₋₁₀ alkyl, optionally substituted aryl or optionally substituted arylalkyl;
- R₁₃ and R₁₄ are independently hydrogen or C₁₋₄ alkyl;
- R₁₇ is C₁₋₄alkyl, aryl, arylalkyl, heteroaryl, heteroarylC₁₋₄alkyl, heterocyclic, or heterocyclicC₁₋₄alkyl, wherein the aryl, heteroaryl and heterocyclic rings may all be optionally substituted;
- R_d is NR₆R₇, alkyl, arylC₁₋₄alkyl, arylC₂₋₄ alkenyl, heteroaryl, heteroaryl-C₁₋₄alkyl, heteroarylC₂₋₄ alkenyl, heterocyclic, heterocyclicC₁₋₄

alkyl, wherein the aryl, heteoaryl and heterocyclic rings may all be optionally substituted;

E is optionally selected from



Compounds of Formula (II) are represented by the structure:



wherein inter alia:

Y is an optionally substituted C₁₋₁₀ alkyl, an optionally substituted C₂₋₁₀ alkenyl, or an optionally substituted C₂₋₁₀ alkynyl; and the remaining variables are as defined above for Formula (I).

15

DETAILED DESCRIPTION OF THE INVENTION

The compounds of Formula (I) and (II) may also be used in association with the veterinary treatment of mammals, other than humans, in need of inhibition of IL-8 or other chemokines which bind to the IL-8 a and b receptors. Chemokine mediated diseases for treatment, therapeutically or prophylactically, in animals include disease states such as those noted herein in the Methods of Treatment section.

25 In compounds of Formula (I) and (II), R is suitably any functional moiety which provides an ionizable hydrogen having a pKa of 10 or less, preferably from

about 3 to 9, more preferably from about 3 to 7. Such functional groups include, but are not limited to, hydroxy, carboxylic acid, thiol, SR_2 , OR_2 , $NH-C(O)R_a$, $C(O)NR_6R_7$, a substituted sulfonamides of the formula $NHS(O)_2R_b$, $S(O)_2NHR_c$, $NHC(X_2)NHR_b$, or a tetrazolyl.

5

Suitably, X_2 is oxygen or sulfur, preferably oxygen.

Suitably, R_2 is a substituted aryl, heteroaryl, or heterocyclic ring, which ring contains the functional moiety providing an ionizable hydrogen having a pK_a of 10 or less.

10

Suitably, R_6 and R_7 are independently hydrogen or a C_{1-4} alkyl group, or R_6 and R_7 together with the nitrogen to which they are attached form a 5 to 7 member ring which ring may optionally contain an additional heteroatom which heteroatom is selected from oxygen, nitrogen or sulfur. This heteroring may be optionally substituted as defined herein.

15

Suitably R_a is an alkyl, aryl, aryl C_{1-4} alkyl, heteroaryl, heteroaryl C_{1-4} alkyl, heterocyclic, or a heterocyclic C_{1-4} alkyl moiety, all of which may be optionally substituted, as defined herein below.

20

Suitably, R_b is a NR_6R_7 , alkyl, aryl, aryl C_{1-4} alkyl, aryl C_{2-4} alkenyl, heteroaryl, heteroaryl C_{1-4} alkyl, heteroaryl C_{2-4} alkenyl, heterocyclic, or heterocyclic C_{1-4} alkyl, a heterocyclic C_{2-4} alkenyl moiety, or camphor, all of which may be optionally substituted one to three times independently by halogen; nitro; halosubstituted C_{1-4} alkyl, such as CF_3 ; C_{1-4} alkyl, such as methyl; C_{1-4} alkoxy, such as methoxy; $NR_9C(O)R_a$; $C(O)NR_6R_7$, $S(O)_3H$, or $C(O)OC_{1-4}$ alkyl. R_b is preferably an optionally substituted phenyl, benzyl, or styryl. When R_b is a heteroaryl preferably it is an optionally substituted thiazole, optionally substituted thienyl, or optionally substituted quinolinyl ring.

25

30

Suitably, R_9 is hydrogen or a C_{1-4} alkyl, preferably hydrogen. Preferably, when the substituent group on the R_b moiety is $NR_9C(O)R_a$, then R_a is preferably an alkyl group, such as methyl.

35

Suitably R_C is hydrogen, alkyl, aryl, arylC₁₋₄alkyl, arylC₁₋₄alkenyl, heteroaryl, heteroarylC₁₋₄alkyl, heteroarylC₁₋₄alkenyl, heterocyclic, or heterocyclic C₁₋₄alkyl, or a heterocyclic C₁₋₄alkenyl moiety, all of which may be optionally substituted one to three times independently by halogen, nitro, halosubstituted C₁₋₄ alkyl, C₁₋₄ alkyl, C₁₋₄ alkoxy, NR₆C(O)R_a, C(O)NR₆R₇, S(O)₃H, or C(O)OC₁₋₄ alkyl. Preferably, R_C is an optionally substituted phenyl.

When R is an OR₂ or SR₂ moiety it is recognized by one of skill in the art that the aryl ring must, therefore, contain the required ionizable hydrogen. The aryl ring may also be additionally substituted, independently, by one to three groups, which groups may also contain an additional ionizable group, and which include but are not limited to, halogen, nitro, halosubstituted C₁₋₄ alkyl, C₁₋₄ alkyl, C₁₋₄ alkoxy, hydroxy, SH, C(O)NR₆R₇, NH-C(O)R_a, NHS(O)₂R_b, S(O)₂NR₆R₇, C(O)OR₈, or a tetrazolyl ring.

Preferably, the functional moiety R is other than a sulfonic acid, either directly or indirectly as a substituent group on the aryl, heteroaryl, or heterocyclic moiety ring, such as in SR₂ or OR₂. More preferably R is OH, SH, or NHS(O)₂R_b.

In compounds of Formula (I), suitably R₁ is independently selected from hydrogen; halogen; nitro; cyano; halosubstituted C₁₋₁₀ alkyl, such as CF₃; C₁₋₁₀ alkyl, such as methyl, ethyl, isopropyl, or n-propyl; C₂₋₁₀ alkenyl; C₁₋₁₀ alkoxy, such as methoxy, or ethoxy; halosubstituted C₁₋₁₀ alkoxy, such as trifluoromethoxy; azide; (CR₈R₈)_q S(O)_tR₄, wherein t is 0, 1 or 2; hydroxy; hydroxy C₁₋₄alkyl, such as methanol or ethanol; aryl, such as phenyl or naphthyl; aryl C₁₋₄ alkyl, such as benzyl; aryloxy, such as phenoxy; aryl C₁₋₄ alkyloxy, such as benzyloxy; heteroaryl; heteroarylalkyl; heteroaryl C₁₋₄ alkyloxy; aryl C₂₋₁₀ alkenyl; heteroaryl C₂₋₁₀ alkenyl; heterocyclic C₂₋₁₀ alkenyl; (CR₈R₈)_qNR₄R₅; C₂₋₁₀ alkenyl C(O)NR₄R₅; (CR₈R₈)_q C(O)NR₄R₅; (CR₈R₈)_q C(O)NR₄R₁₀; S(O)₃H; S(O)₃R₈; (CR₈R₈)_q C(O)R₁₁; C₂₋₁₀ alkenyl C(O)R₁₁; C₂₋₁₀ alkenyl C(O)OR₁₁; C(O)R₁₁; (CR₈R₈)_q C(O)OR₁₂; (CR₈R₈)_qOC(O)R₁₁; (CR₈R₈)_q NR₄C(O)R₁₁, (CR₈R₈)_q NHS(O)₂R₁₇, (CR₈R₈)_qS(O)₂NR₄R₅; or two R₁ moieties together may form O-(CH₂)_sO- or a 5 to 6 membered unsaturated ring; and s is an integer having a value of 1 to 3. The aryl, arylalkyl, arylalkenyl, heteroaryl, heteroarylalkyl, heteroarylalkenyl, heterocyclic, heterocyclicalkyl, and

heterocyclicalkenyl moieties may all be optionally substituted as defined herein below.

Suitably, q is 0, or an integer having a value of 1 to 10.

5

When R₁ forms a dioxybridge, s is preferably 1. When R₁ forms an additional unsaturated ring, it is preferably 6 membered resulting in a naphthylene ring system. This naphthylene ring may be substituted independently, 1 to 3 times by the other R₁ moieties as defined above.

10

Suitably, R₄ and R₅ are independently hydrogen, optionally substituted C₁₋₄ alkyl, optionally substituted aryl, optionally substituted aryl C₁₋₄alkyl, optionally substituted heteroaryl, optionally substituted heteroaryl C₁₋₄alkyl, heterocyclic, heterocyclicC₁₋₄ alkyl, or R₄ and R₅ together with the nitrogen to which they are attached form a 5 to 7 member ring which may optionally comprise an additional heteroatom selected from O/N/S.

15

Suitably, R₈ is independently selected from hydrogen or C₁₋₄ alkyl.

20

Suitably, R₁₀ is C₁₋₁₀ alkyl C(O)₂R₈, such as CH₂C(O)₂H or CH₂C(O)₂CH₃.

Suitably, R₁₁ is hydrogen, C₁₋₄ alkyl, aryl, aryl C₁₋₄ alkyl, heteroaryl, heteroaryl C₁₋₄alkyl, heterocyclic, or heterocyclic C₁₋₄alkyl.

25

Suitably, R₁₂ is hydrogen, C₁₋₁₀ alkyl, optionally substituted aryl or optionally substituted arylalkyl.

Suitably, R₁₇ is C₁₋₄alkyl, aryl, arylalkyl, heteroaryl, heteroarylC₁₋₄alkyl, heterocyclic, or heterocyclicC₁₋₄alkyl, wherein the aryl, heteroaryl and heterocyclic rings may all be optionally substituted.

30

Preferably R₁ is halogen, cyano, nitro, CF₃, C(O)NR₄R₅, alkenyl C(O)NR₄R₅, C(O) R₄R₁₀, alkenyl C(O)OR₁₂, heteroaryl, heteroarylalkyl, heteroaryl alkenyl, or S(O)NR₄R₅, and preferably R₄ and R₅ are both hydrogen or

35

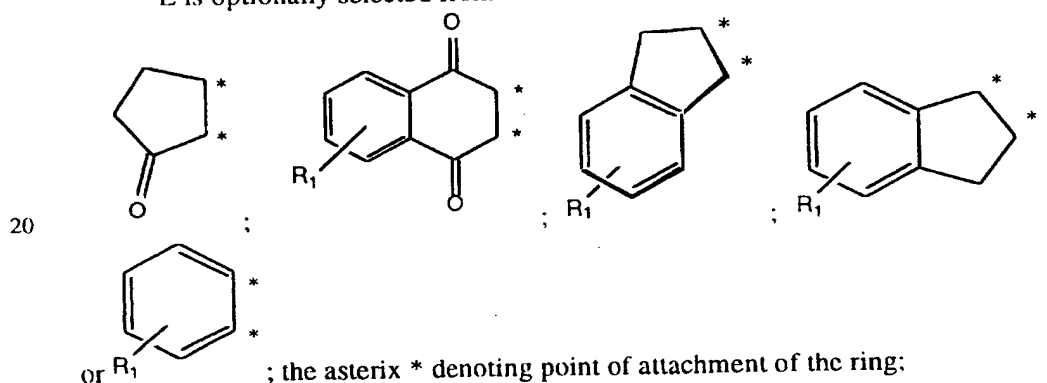
one is phenyl. A preferred ring substitution for R_1 is in the 4-position of the phenyl ring.

When R is OH, SH or NSO_2R_b than R_1 is preferably substituted in the 3-
 5 position, the 4- position or di substituted in the 3,4- position. The substituent group is suitably an electron withdrawing moiety. Preferably when R is OH, SH or NSO_2R_b , than R_1 is nitro, halogen, cyano, trifluoromethyl group, $C(O)NR_4R_5$.

When R is carboxylic acid, than R_1 is preferably hydrogen, or R_1 is
 10 preferably substituted in the 4-position, more preferably substituted by trifluoromethyl or chloro.

In compounds of Formula (I), the benzene ring may be optionally substituted
 15 by the group E. If E is not present, than the two positions marked by the asterix may be hydrogen, or the group R_1 . The E ring is denoted by its point of attachment through the asterix (*). The E ring may also be substituted by the R_1 moiety, independently, in any ring, saturated or unsaturated.

E is optionally selected from



In compounds of Formula (I), suitably R_{13} and R_{14} are independently
 25 hydrogen or C_{1-4} alkyl which may be straight or branched as defined herein: v is 0, or an integer having a value of 1 to 4, preferably $v = 0$.

In compounds of Formula (I), suitably the saturated ring system wherein n is an integer having a value of 1 to 3 is preferably a six membered ring system. The ring system is optionally substituted by Y as defined below.

- 5 In compounds of Formula (I), suitably Y is independently selected from hydrogen; halogen; nitro; cyano; halosubstituted C₁₋₁₀ alkyl; C₁₋₁₀ alkyl; C₂₋₁₀ alkenyl; C₁₋₁₀ alkoxy; halosubstituted C₁₋₁₀ alkoxy; azide; (CR₈R₈)_q S(O)_tR₄; hydroxy; hydroxyC₁₋₄alkyl; aryl; aryl C₁₋₄ alkyl; aryloxy; arylC₁₋₄ alkyloxy; heteroaryl; heteroarylalkyl; heteroaryl C₁₋₄ alkyloxy; heterocyclic, heterocyclic
- 10 C₁₋₄alkyl; aryl C₂₋₁₀ alkenyl; heteroaryl C₂₋₁₀ alkenyl; heterocyclic C₂₋₁₀ alkenyl; (CR₈R₈)_q NR₄R₅; C₂₋₁₀ alkenyl C(O)NR₄R₅; (CR₈R₈)_q C(O)NR₄R₅; (CR₈R₈)_q C(O)NR₄R₁₀; S(O)₃H; S(O)₃R₈; (CR₈R₈)_q C(O)R₁₁; C₂₋₁₀ alkenyl C(O)R₁₁; C₂₋₁₀ alkenyl C(O)OR₁₁; (CR₈R₈)_q C(O)OR₁₂; (CR₈R₈)_q OC(O)R₁₁; (CR₈R₈)_q NR₄C(O)R₁₁, (CR₈R₈)_q NHS(O)₂R_d, (CR₈R₈)_q S(O)₂NR₄R₅ or two
- 15 Y moieties together may form O-(CH₂)_sO- or a 5 to 6 membered unsaturated ring. When Y forms a dioxybridge, s is preferably 1. When Y forms an additional unsaturated ring, it is preferably 6 membered resulting in a naphthylene ring system. This naphthylene ring may be substituted 1 to 3 times by other Y moieties as defined above. The aryl, arylalkyl, arylalkenyl, heteroaryl, heteroarylalkyl,
- 20 heteroarylalkenyl, heterocyclic, heterocyclicalkyl, and heterocyclicalkenyl moieties noted above may all be optionally substituted as defined herein.

- Suitably, R_d is a NR₆R₇-, alkyl, aryl C₁₋₄ alkyl, arylC₂₋₄ alkenyl, heteroaryl, heteroaryl-C₁₋₄alkyl, heteroarylC₂₋₄ alkenyl, heterocyclic,
- 25 heterocyclicC₁₋₄ alkyl, or heterocyclic C₂₋₄ alkenyl moiety, wherein the aryl, arylalkyl, arylalkenyl, heteroaryl, heteroarylalkyl, heteroarylalkenyl, heterocyclic, and heterocyclicalkyl, and heterocyclicalkenyl moieties noted above may all be optionally substituted as defined herein.

- 30 Y is preferably hydrogen, aryl, such as phenyl; aryloxy, such as phenoxy; arylalkyl, such as benzyl, or phenethyl; or arylalkyloxy, such as benzyloxy, or phenethyloxy. Y is more preferably mono substituted in the 2'- position of the six membered ring. Preferably when R is OH, SH, or NSO₂R_b, Y is preferably mono-
- 35 substituted in the 2'-position or 3'- position, with the 4'- preferably being unsubstituted. If the ring is disubstituted, when R is OH, SH, or NSO₂R_b, substituents are preferably in the 2' or 3' position of a monocyclic ring. While both

R₁ and Y can both be hydrogen, it is preferred that at least one of the rings be substituted.

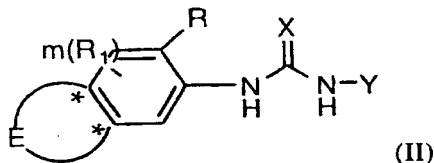
In compounds of Formula (I), X is suitably oxygen or sulfur, preferably oxygen.

Exemplified compounds of Formula (I) include:

N-Cyclohexyl-N'-(2-hydroxy-4-nitrophenyl)urea
 (+/-)-Trans-N-(2-Benzoyloxycyclohexyl)-N'-(2-hydroxy-4-nitrophenyl) urea
 10 N-trans-(2-Hydroxycyclohexyl)-N'-(2-hydroxy-4-nitrophenyl)urea mp 144.6-145.2 C
 N-trans-(2-Benzoxycyclopentyl)-N'-(2-hydroxy-4-nitrophenyl)urea mp 53.4-54.4 C
 N-trans-(2-Methoxycyclohexyl)-N'-(2-hydroxy-4-nitrophenyl)urea mp 88.8-89.6 C

Another aspect of the present invention are the novel compounds of Formula (II), or a pharmaceutically acceptable salt thereof, as described below, which are also useful in inhibiting the binding of IL-8 to its receptors in a mammal in need thereof. This invention also relates to the pharmaceutical compositions comprising a compound of Formula (II) and a pharmaceutically acceptable diluent or carrier. Compounds of Formula (II) are also useful for treating a chemokine mediated disease, wherein the chemokine is one which binds to an IL-8 α or β receptor and which method comprises administering an effective amount of a compound of Formula (II) or a pharmaceutically acceptable salt thereof. Compounds of Formula (I) and (II) are used interchangeably in the Methods of Treatment section.

Compounds of Formula (II) useful in the present invention are represented by the structure:



wherein

X is oxygen or sulfur;

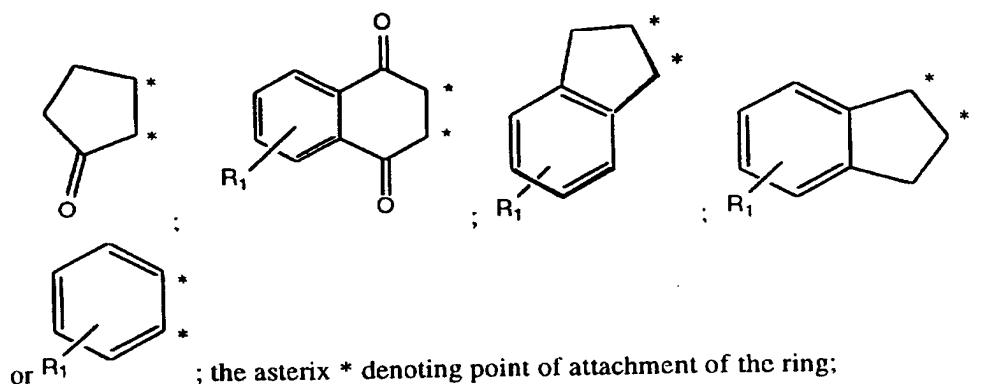
30 R is any functional moiety having an ionizable hydrogen and a pKa of 10 or less;

R₁ is independently selected from hydrogen; halogen; nitro; cyano; halosubstituted

C₁₋₁₀ alkyl; C₁₋₁₀ alkyl; C₂₋₁₀ alkenyl; C₁₋₁₀ alkoxy; halosubstituted C₁₋₁₀

alkoxy; azide; (CR₈R₈)_q S(O)_tR₄; hydroxy; hydroxy C₁₋₄alkyl; aryl; aryl C₁₋₄

- alkyl; aryloxy; aryl C₁₋₄ alkyloxy; heteroaryl; heteroarylalkyl; heterocyclic, heterocyclic C₁₋₄alkyl; heteroaryl C₁₋₄ alkyloxy; aryl C₂₋₁₀ alkenyl; heteroaryl C₂₋₁₀ alkenyl; heterocyclic C₂₋₁₀ alkenyl; (CR₈R₈)_qNR₄R₅; C₂₋₁₀ alkenyl C(O)NR₄R₅; (CR₈R₈)_q C(O)NR₄R₅; (CR₈R₈)_q C(O)NR₄R₁₀; S(O)₃H;
 5 S(O)₃R₈; (CR₈R₈)_q C(O)R₁₁; C₂₋₁₀ alkenyl C(O)R₁₁; C₂₋₁₀ alkenyl C(O)OR₁₁(CR₈R₈)_q C(O)OR₁₂; (CR₈R₈)_q OC(O) R₁₁; (CR₈R₈)_qNR₄C(O)R₁₁, (CR₈R₈)_q NHS(O)₂R₁₇, (CR₈R₈)_q S(O)₂NR₄R₅; or two R₁ moieties together may form O-(CH₂)₅O- or a 5 to 6 membered unsaturated ring;
- 10 q is 0, or an integer having a value of 1 to 10;
 s is an integer having a value of 1 to 3;
 t is 0, or an integer having a value of 1 or 2;
 m is an integer having a value of 1 to 3;
 R₄ and R₅ are independently hydrogen, optionally substituted C₁₋₄ alkyl, optionally
 15 substituted aryl, optionally substituted aryl C₁₋₄alkyl, optionally substituted heteroaryl, optionally substituted heteroaryl C₁₋₄alkyl, heterocyclic, heterocyclic C₁₋₄ alkyl, or R₄ and R₅ together with the nitrogen to which they are attached form a 5 to 7 member ring which may optionally comprise an additional heteroatom selected from oxygen, nitrogen, or sulfur;
- 20 Y is an optionally substituted C₁₋₁₀ alkyl, an optionally substituted C₂₋₁₀ alkenyl, or an optionally substituted C₂₋₁₀ alkynyl;
 R₈ is independently selected from hydrogen or C₁₋₄ alkyl;
 R₁₀ is C₁₋₁₀ alkyl C(O)₂R₈;
 R₁₁ is hydrogen, C₁₋₄ alkyl, optionally substituted aryl, optionally substituted aryl
 25 C₁₋₄alkyl, optionally substituted heteroaryl, optionally substituted heteroarylC₁₋₄alkyl, optionally substituted heterocyclic, or optionally substituted heterocyclicC₁₋₄alkyl;
 R₁₂ is hydrogen, C₁₋₁₀ alkyl, optionally substituted aryl or optionally substituted arylalkyl;
- 30 R₁₇ is C₁₋₄alkyl, aryl, arylalkyl, heteroaryl, heteroarylC₁₋₄alkyl, heterocyclic, or heterocyclicC₁₋₄alkyl, wherein the aryl, heteroaryl and heterocyclic rings may all be optionally substituted;
 E is optionally selected from



provided that when R is OH, R_1 is 4-nitro, and E is a bond, then Y is other
 5 than ethoxycarbonyl-2-ethyl propyl, 1-isopropyl 2- benzyloxyethyl; 2-
 ethoxycarbonyl ethyl, ethylisopropyl ether, 1-methyl-2-phenylbenzoxyethyl, 1-
 methyl-2-phenylbenzoxyethyl, 2-carboxyethyl or 1-phenyl-2-benzoxyethyl;
 or a pharmaceutically acceptably salt thereof.

10 In compounds of Formula (II), the variables R, R_1 , X, m, q, t, s, R_4 , R_5 , R_8 ,
 R_{10} , R_{11} , R_{12} , R_{17} , and E, etc., are as defined above for compounds of Formula
 (I).

For compounds of Formula (II), Y is suitably an optionally substituted C_{1-10}
 15 alkyl, an optionally substituted C_{2-10} alkenyl, or an optionally substituted C_{2-10}
 alkynyl moiety. These alkyl, alkenyl and alkynyl moieties may be optional
 substituted one or more times, preferably 1 to 3 times, independently by halogen;
 nitro; cyano; halosubstituted C_{1-10} alkyl, such as trifluoromethyl; C_{1-10} alkoxy;
 halosubstituted C_{1-10} alkoxy; $S(O)_t R_4$; hydroxy; hydroxy C_{1-4} alkyl; aryloxy;
 20 aryl C_{1-4} alkyloxy; heteroaryloxy; heteroaryl C_{1-4} alkyloxy; heterocyclic,
 heterocyclic C_{1-4} alkyl; heterocyclic oxy; heterocyclic C_{1-4} alkyloxy; $NR_4 R_5$;
 $C(O)NR_4 R_5$; $C(O)NR_4 R_{10}$; $S(O)_3 H$; $S(O)_3 R_8$; $C(O)R_{11}$; $C(O)OR_{12}$; $OC(O)R_{11}$;
 and $NR_4 C(O)R_{11}$.

25 When Y is an optionally substituted C_{2-10} alkenyl, or an optionally
 substituted C_{2-10} alkynyl these moieties may also, in addition to those moieties
 above, also be optionally substituted with an optionally substituted aryl; optionally

substituted aryl C₁₋₄ alkyl; optionally substituted heteroaryl; and optionally substituted heteroarylalkyl, as defined below.

Y is preferably allyl, C₁₋₁₀ alkyl, ethoxy carbonyl ethyl, dimethylacetal, 2-methoxy isopropyl, or 2-methoxy ethyl.

Exemplified compounds of Formula (II) include:

- N-Allyl-N'-(2-hydroxy-4-nitrophenyl)urea
- N-t-Butyl-N'-(2-hydroxy-4-nitrophenyl)urea
- 10 N-[2-(Ethoxycarbonyl)propyl]-N'-(2-hydroxy-4-nitrophenyl)urea
- N-Isopropyl-N'-(2-hydroxy-4-nitrophenyl)urea
- N-(1-(Ethoxycarbonyl)ethyl)-N'-(2-hydroxy-4-nitrophenyl)urea
- N-(Dimethylacetal)-N'-(2-hydroxy-4-nitrophenyl)urea
- N-(2-Methoxyethyl)-N'-(2-hydroxy-4-nitrophenyl)urea
- 15 N-(2-Benzyloxypropyl)-N'-(2-hydroxy-4-nitrophenyl)urea
- N-(2-methoxyisopropyl)-N'-(2-hydroxy-4-nitrophenyl)urea
- N-(1-carbonyl-2-methylpropyl)-N'-(2-hydroxy-4-nitrophenyl)urea
- N-(1,1-Dimethyl-2-benzyloxyethyl)-N'-(2-hydroxy-4-nitrophenyl)urea
- N-(1,2-dimethyl-2-benzyloxyethyl)-N'-(2-hydroxy-4-nitrophenyl)urea
- 20 N-(2-benzenesulfonylamino-4-cyanophenyl)-N'-(isopropyl)urea
- N-(2-Hydroxy-4-nitrophenyl)-N'-(2-methoxyethyl)urea
- N-(2-Hydroxy-4-nitrophenyl)-N'-(2-benzyloxypropyl)urea
- N-(2-Hydroxy-4-nitrophenyl)-N'-(2-methoxyisopropyl)urea
- N-(2-Hydroxy-4-nitrophenyl)-N'-(1-carbonyl-2-methylpropyl)urea
- 25 N-(2-Hydroxy-4-nitrophenyl)-N'-(1,2-dimethyl-2-benzyloxyethyl)urea
- N-(2-Benzenesulfonylamino-4-cyanophenyl)-N'-(isopropyl)urea

As used herein, "optionally substituted" unless specifically defined shall mean such groups as halogen, such as fluorine, chlorine, bromine or iodine; hydroxy; hydroxy substituted C₁₋₁₀alkyl; C₁₋₁₀ alkoxy, such as methoxy or ethoxy; S(O)_{m'} C₁₋₁₀ alkyl, wherein m' is 0, 1 or 2, such as methyl thio, methyl

30 sulfinyl or methyl sulfonyl; amino, mono & di-substituted amino, such as in the NR₄R₅ group; NHC(O)R₄; C(O)NR₄R₅; C(O)OH; S(O)₂NR₄R₅; NHS(O)₂R₁₅, C₁₋₁₀ alkyl, such as methyl, ethyl, propyl, isopropyl, or t-butyl; halosubstituted C₁₋₁₀ alkyl, such CF₃; an optionally substituted aryl, such as phenyl, or an optionally

35 substituted arylalkyl, such as benzyl or phenethyl, optionally substituted heterocyclic, optionally substituted heterocyclicalkyl, optionally substituted heteroaryl, optionally

substituted heteroaryl alkyl, wherein these aryl, heteroaryl, or heterocyclic moieties may be substituted one to two times by halogen; hydroxy; hydroxy substituted alkyl; C₁₋₁₀ alkoxy; S(O)_mC₁₋₁₀ alkyl; amino, mono & di-substituted amino, such as in the NR₄R₅ group; C₁₋₁₀ alkyl, or halosubstituted C₁₋₁₀ alkyl, such as CF₃.

- 5 R₁₅ is suitably C₁₋₄ alkyl, aryl, aryl C₁₋₄alkyl, heteroaryl, heteroarylC₁₋₄alkyl, heterocyclic, or heterocyclicC₁₋₄alkyl.

- Suitable pharmaceutically acceptable salts are well known to those skilled in the art and include basic salts of inorganic and organic acids, such as hydrochloric
10 acid, hydrobromic acid, sulphuric acid, phosphoric acid, methane sulphonic acid, ethane sulphonic acid, acetic acid, malic acid, tartaric acid, citric acid, lactic acid, oxalic acid, succinic acid, fumaric acid, maleic acid, benzoic acid, salicylic acid, phenylacetic acid and mandelic acid. In addition, pharmaceutically acceptable salts of compounds of Formula (I) may also be formed with a pharmaceutically
15 acceptable cation, for instance, if a substituent group comprises a carboxy moiety. Suitable pharmaceutically acceptable cations are well known to those skilled in the art and include alkaline, alkaline earth, ammonium and quaternary ammonium cations.

- 20 The following terms, as used herein, refer to:

- "halo" - all halogens, that is chloro, fluoro, bromo and iodo.
- "C₁₋₁₀alkyl" or "alkyl" - both straight and branched chain radicals of 1 to 10 carbon atoms, unless the chain length is otherwise limited, including, but not limited to, methyl, ethyl, *n*-propyl, *iso*-propyl, *n*-butyl, *sec*-butyl, *iso*-butyl, *tert*-
25 butyl, *n*-pentyl and the like.
- The term "cycloalkyl" is used herein to mean cyclic radicals, preferably of 3 to 8 carbons, including but not limited to cyclopropyl, cyclopentyl, cyclohexyl, and the like.
- The term "alkenyl" is used herein at all occurrences to mean straight or
30 branched chain radical of 2-10 carbon atoms, unless the chain length is limited thereto, including, but not limited to ethenyl, 1-propenyl, 2-propenyl, 2-methyl-1-propenyl, 1-butenyl, 2-butenyl and the like.
- "aryl" - phenyl and naphthyl;
- "heteroaryl" (on its own or in any combination, such as "heteroaryloxy", or
35 "heteroaryl alkyl") - a 5-10 membered aromatic ring system in which one or more rings contain one or more heteroatoms selected from the group consisting of N, O or

S, such as, but not limited, to pyrrole, pyrazole, furan, thiophene, quinoline, isoquinoline, quinazolinyl, pyridine, pyrimidine, oxazole, thiazole, thiadiazole, triazole, imidazole, or benzimidazole.

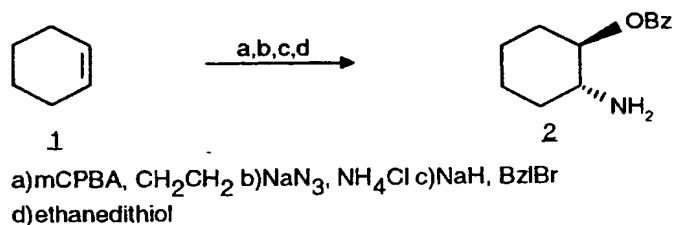
- "heterocyclic" (on its own or in any combination, such as
- 5 "heterocyclicalkyl") - a saturated or partially unsaturated 4-10 membered ring system in which one or more rings contain one or more heteroatoms selected from the group consisting of N, O, or S; such as, but not limited to, pyrrolidine, piperidine, piperazine, morpholine, tetrahydropyran, or imidazolidine.
- The term "arylalkyl" or "heteroarylalkyl" or "heterocyclicalkyl" is used
- 10 herein to mean C₁-10 alkyl, as defined above, attached to an aryl, heteroaryl or heterocyclic moiety, as also defined herein, unless otherwise indicated.
- "sulfinyl" - the oxide S (O) of the corresponding sulfide, the term "thio" refers to the sulfide, and the term "sulfonyl" refers to the fully oxidized S(O)₂ moiety.
- 15 • The term "wherein two R₁ moieties (or two Y moieties) may together form a 5 or 6 membered unsaturated ring" is used herein to mean the formation of a naphthylene ring system or a phenyl moiety having attached a 6 membered partially unsaturated ring such as a C₆ cycloalkenyl, i.e hexene, or a C₅ cycloalkenyl moiety, cyclopentene. It is recognized that in cases where the E ring is present it is unlikely
- 20 that two R₁ moieties will form another ring.

The compounds of Formula (I) and (II) may be obtained by applying synthetic procedures, some of which are illustrated in the Schemes below. The synthesis provided for in these Schemes is applicable for the producing compounds

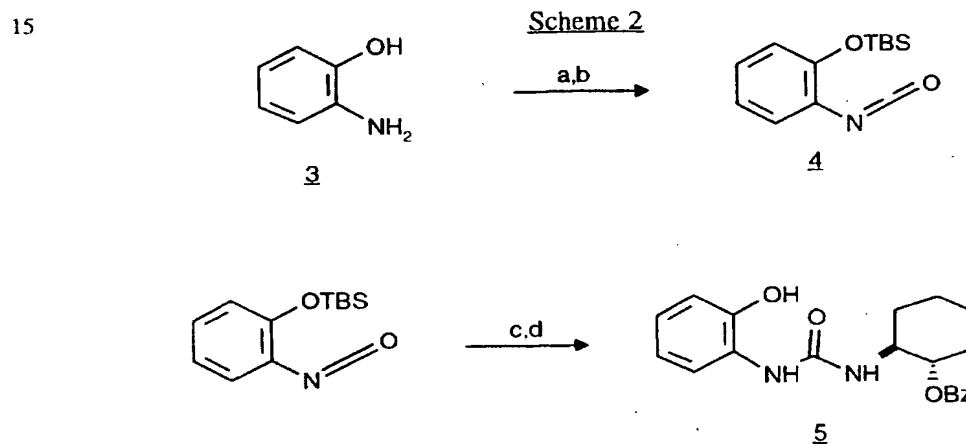
25 of Formula (I) and (II) having a variety of different R, R₁, and Aryl groups which are reacted, employing optional substituents which are suitably protected, to achieve compatibility with the reactions outlined herein. Subsequent deprotection, in those cases, then affords compounds of the nature generally disclosed. Once the urea nucleus has been established, further compounds of these formulas may be prepared

30 by applying standard techniques for functional group interconversion, well known in the art. While the schemes are shown with compounds only of Formula (I), wherein w=2, this is merely for illustration purposes only.

Scheme 1



The alkoxy amines can be synthesized from the corresponding alkene. The alkene can be epoxidized using a peracid like mCPBA or a metal epoxidation catalyst like manganese (salen) in the presence of a stoichiometric oxidant like sodium perchlorate. The epoxide can then be opened with sodium azide in a polar solvent such as methanol or DMF to form the trans azido alcohol. The alcohol can be alkylated using an alkylating agent such as benzyl bromide in the presence of a base such as triethyl amine or sodium hydride. The alcohol can also be inverted to form the cis alcohol using Mitsunobu conditions. The azide can then be reduced under a variety of reagents such as ethanedithiol, triphenylphosphine or lithium aluminum hydride to form 2- scheme 1. Alternative reagents to benzyl bromide, such as alkyl and substituted alkyl bromides may be utilized.

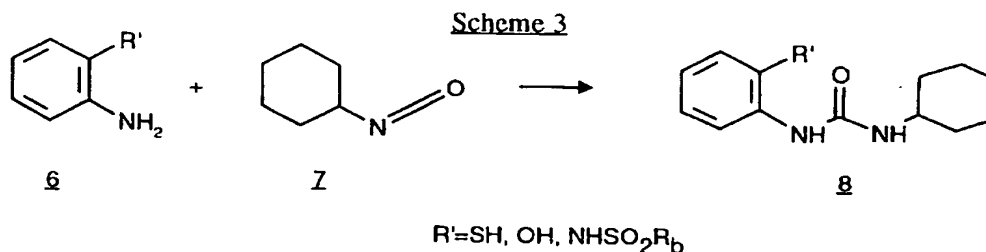


a) TBSCl, imid b) triphosgene, NaHCO₃ c) 2, toluene d) Et₃N.HF, CH₃CN

The 2-hydroxy aniline can be protected by reagents known in the art such as tert(butyl)dimethylsilyl chloride and imidazole in an aprotic solvent like DMF (scheme 2). The aniline can then be reacted with a phosgene equivalent like triphosgene or carbonyl diimidazole in the presence of a base such as sodium bicarbonate to form the isocyanate 4 (or with thiophosgene to form the thio

isocyanate). This isocyanate can then be condensed with the desired amine 2 which can either be purchased commercially or synthesized by the method outlined in scheme 1. The compound can then be deprotected by standard conditions such as triethylamine hydrofluoride to form the urea 5.

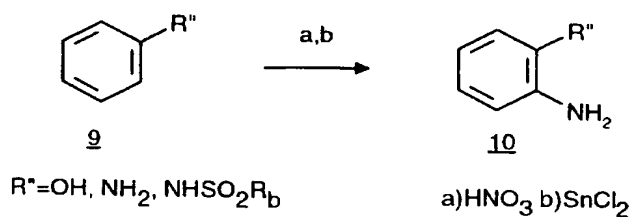
5



Alternatively the urea can be synthesized from the commercially available hydroxyaniline and the corresponding isocyanate (scheme 3). This isocyanate can either purchased commercially or synthesized from the amine and a phosgene equivalent like triphosgene or carbonyl diimidazole in the presence of a base such as sodium bicarbonate. R_b is as defined in Formula (I).

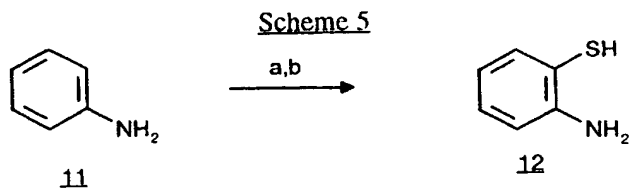
Ortho substituted phenyl ureas shown in 6-scheme 3 may be prepared by standard conditions involving the condensation of commercially available ortho substituted aniline (Aldrich Chemical Co., Milwaukee, Wi) with the commercially available optionally substituted aryl isocyanate (Aldrich Chemical Co., Milwaukee, Wi) in an aprotic solvent (DMF, toluene). When the 1-(RSO_2NH)₂-(NH_2)Ph is not commercially available it can be made by treating the commercially available $\text{R}_b\text{SO}_2\text{Cl}$ with the corresponding 2-phenylene diamine in the presence of an base like triethyl amine or NaH in an aprotic solvent (like methylene chloride or DMF).

Scheme 4



If the desired 2-substituted aniline 10-scheme 4, is not commercially available the corresponding nitro compound can be prepared from 9-scheme 4, under standard nitration conditions (using HNO_3 or BF_4NO_3) at 23 °C. The nitro

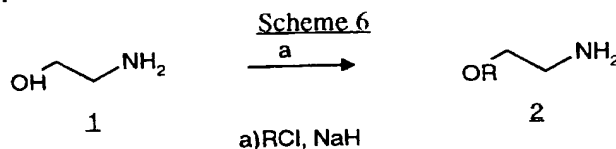
compound is then reduced to the corresponding aniline using SnCl_2 in EtOH (or alternately H_2/Pd or LiAlH_4).



a) NH_4SCN , Br b) NaOH

5 If the desired 2-amino benzenethiol 11-scheme 5 is not commercially available it can be synthesized by reaction of the phenyl aniline with the thiocyanate anion in the presence of an oxidant (like bromine) to produce the 2-amino benzthiazole. This thiazole can then be hydrolyzed to the desired 2-amino
10 benzenethiol 12-scheme 5 with a strong base like NaOH in a protic solvent (i.e., EtOH).

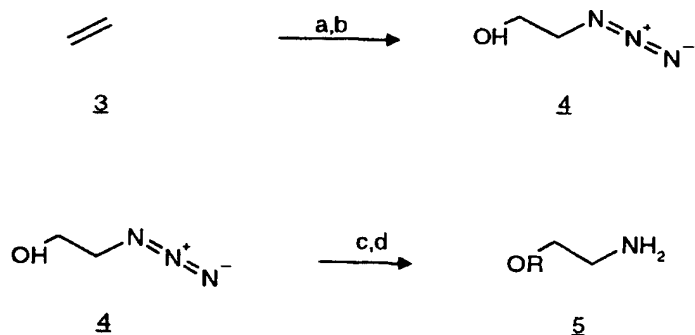
Methods of Preparation for Compounds of Formula (II):



a) RCl , NaH

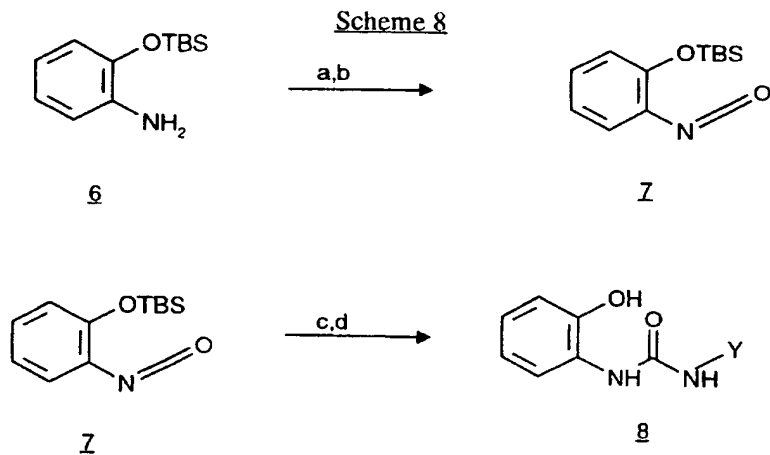
15 If the alkoxyamine is not commercially available it can be synthesized from the corresponding amino alcohol by alkylation using an alkyl chloride and a base such as sodium hydride to form 2 (scheme 6). Alternatively the alkoxy amine can be synthesized from the cooresponding alkene as shown in scheme 7. The alkene
20 can be epoxidized by standard conditions such as a peracid or using a stiochiometric oxidant like sodium perchlorate in the presence of a mctal catalyst like maganese(salen). This epoxide can then be opened by an azide salt, such as sodium azide to form 4, scheme 7. This hydroxy azide can then be alkylated using an alkyl halide(RX) in the presence of a base (such as triethyl amine or sodium hydride).
25 Finally the azide can be reduced under standard conditions such as a thiol, triarylphosphine, or hydrogenation with a palladium catalyst to form 5, scheme 7.

Scheme 7



a) mCPBA b) NaN₃ c) NaH, RCl d) ethanedithiol

Once the desired alkyl amine (YNH₂) has been synthesized the urea can be synthesized by a variety of methods. Some of these different methods are described below.

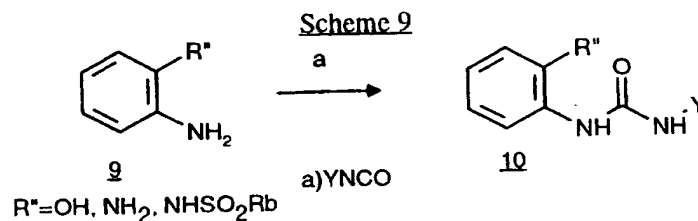


a) TBSCl, imid b) triphosgene, NaHCO₃ c) YNH₂ d) Et₃N·HF

The 2-hydroxy aniline can be protected by reagents known in the art such as tert(butyl)dimethylsilyl chloride and imidazole in an aprotic solvent like DMF (scheme 8). The aniline can then be reacted with a phosgene equivalent like triphosgene or carbonyl diimidazole in the presence of a base such as sodium bicarbonate to form the isocyanate 7. This isocyanate can then be condensed with the

desired amine (YNH₂) which can either be purchased commercially or synthesized by the method outlined in schemes 1 and 2. The protected phenol can then be deprotected by standard conditions such as triethyl amine hydrofluoride to form the urea 8 (scheme 8).

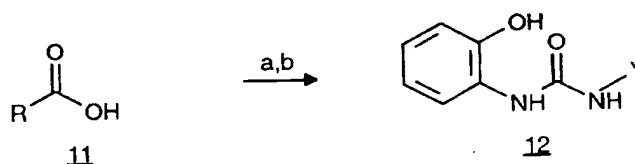
5



Alternatively the urea can be synthesized from the commercially available hydroxyaniline and the corresponding isocyanate (scheme 9). This isocyanate can either purchased commercially or synthesized from the amine and a phosgene equivalent like triphosgene or carbonyl diimidazole in the presence of a base such as sodium bicarbonate. When the 1-(RSO₂NH)2-(NH₂)Ph is not commercially available it can be made by treating the commercially available R_bSO₂Cl with the corresponding 2-phenylene diamine in the presence of an base like triethyl amine or NaH in an aprotic solvent (like methylene chloride or DMF).

15

Scheme 10

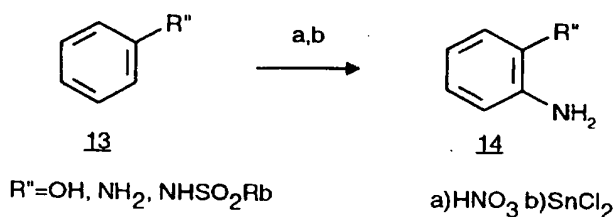


20

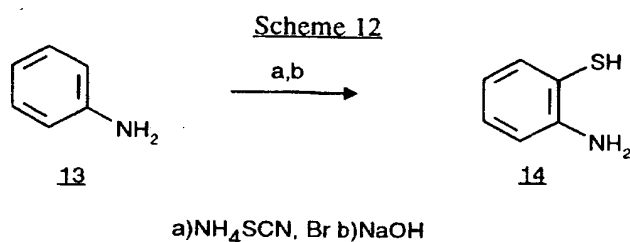
Alternatively the isocyanate can be synthesized from the corresponding carboxylic acid using the Curtius rearrangement (dppa and triethyl amine, or oxalyl chloride followed by sodium azide, scheme 10). This isocyanate can then be condensed with the commercially available hydroxy aniline to form urea 12 (scheme 10).

25

Scheme 11



If the desired hydroxy aniline is not commercially available it can be synthesized by nitration of the corresponding phenol with a nitrating agent such as nitric acid or nitrosonium tetrafluoroborate (scheme 9). This nitro group can then be reduced to form the hydroxy aniline using conditions standard in the art such as tin chloride, or hydrogen and palladium on carbon to form the hydroxy aniline 14 (scheme 11).



If the desired 2-amino benzenethiol 14-scheme 12 is not commercially available it can be synthesized by reaction of the phenyl aniline with the thiocyanate anion in the presence of an oxidant (like bromine) to produce the 2-amino benzthiazole. This thiazole can then be hydrolyzed to the desired 2-amino benzenethiol 12-scheme 10 with a strong base like NaOH in a protic solvent (i.e., EtOH).

Pharmaceutically acceptable salts of compounds of Formula (I) and (II) may be obtained in known manner, for example by treatment thereof with an appropriate amount of acid or base in the presence of a suitable solvent.

Synthesis of the cyano nitrophenol intermediate may be produced as described below. Numerous conversions of aryl halides to aryl cyano derivatives with copper (I) cyanide have been published. However, no examples of an aryl ring with a hydroxy group present were mentioned. Several attempts to obtain a cyano phenol moiety with published results failed. Using known conditions of elevated temperatures, greater than 170 °C, such as from 180 to 210 °C did not yield

displacement of the halogen to a cyano moiety. Standard bases, such as DMF and pyridine further provided no desired product. Intermediates such as 2-amino-5-fluorophenol, 2-nitro-5-fluorophenol, 2-nitro-5-methyl-6-bromophenol were tried with a change of halogens, from fluorine to chlorine to bromine, and with use of copper (I) cyanide. The use of a bromine derivative, such as 2-nitro-5-methyl-6-bromophenol, with dimethylformamide and using triethylamine with a catalytic amount of dimethylamino pyridine and copper (I) cyanide at reduced temperatures, i.e. <100 °C, preferably 60 to about 80 °C for reduced times from standardized procedures, i.e., < 18 hours, preferably about 4 to 6 hours yield the desired products for use herein.

In the Examples, all temperatures are in degrees Centigrade (°C). Mass spectra were performed upon a VG Zab mass spectrometer using fast atom bombardment, unless otherwise indicated. ¹H-NMR (hereinafter "NMR") spectra were recorded at 250 MHz or 400MHz using a Bruker AM 250 or Am 400 spectrometer, respectively. Multiplicities indicated are: s=singlet, d=doublet, t=triplet, q=quartet, m=multiplet and br indicates a broad signal. Sat. indicates a saturated solution, equiv. indicates the proportion of a molar equivalent of reagent relative to the principal reactant.

Flash chromatography is run over Merck Silica gel 60 (230 - 400 mesh).

SYNTHETIC EXAMPLES

The invention will now be described by reference to the following examples which are merely illustrative and are not to be construed as a limitation of the scope of the present invention. All temperatures are given in degrees centigrade, all solvents used herein are of the highest available purity and all reactions are run under anhydrous conditions in an argon atmosphere unless otherwise indicated.

Illustrative Experimental Examples

General Method A: Synthesis of N-phenyl, N'-phenyl urea To a solution of phenyl isocyanate (1.0 equiv.) in dimethyl formamide (1mL) the corresponding aniline (1.0 equiv.) was added. The reaction mixture was stirred at 80°C until complete (24-48 hours.), then the solvent was removed under vacuum. The purifications, yields and spectral characteristics for each individual compound are listed below.

- General Method B: Synthesis of sulfonamide** The ortho substituted aniline (1 equiv.), triethyl amine (1 equiv.) and the desired sulfonyl chloride (1 equiv.) were combined in methylene chloride and allowed to stir at about 23 °C until complete (12-36h). The reaction mixture was partitioned between water and methylene chloride. The organic layer was separated and dried over magnesium sulfate, filtered and concentrated *in vacuo*. The purifications of each compound are listed below.

Example 1

10 Preparation of N-Cyclohexyl-N'-(2-hydroxy-4-nitrophenyl)urea

- To a solution of cyclohexyl isocyanate (400 mg, 3.19 mmol) in toluene, 2-amino-5-nitrophenol (492 mg, 3.19 mmol) was added. The reaction mixture was stirred at 80°C for 24 hours, then cooled to room temperature. The product was purified by precipitation from toluene and filtering (752 mg, 93 %). m.p: 185.0-186.0°C; EI-MS m/z 280 (M+H)⁺.

Example 2

Preparation of Trans-N-(2-Benzylloxycyclohexyl)-N'-(2-hydroxy-4-nitrophenyl) urea

20 a) Preparation of 2-Azidocyclohexylalcohol

- A mixture of cyclohexene oxide (2 g, 20.4 mmol), sodium azide (1.86 g, 30.6 mmol), and ammonium chloride (2.16 g, 40.8 mmol) in methanol /water (61mL/6mL) was heated to 72 °C for 16 hours. The reaction mixture was then cooled to room temperature. All the solvent was evaporated. The residue was partitioned between ethyl acetate and water. The organic layer was dried over MgSO₄, filtered and concentrated under reduced pressure to give pure product. (2.3 g, 80 %). EI-MS m/z 242 (M+H)⁺.

b) Preparation of trans-2-benzylloxycyclohexylazide

- 30 To a solution of 2-azidocyclohexylalcohol (1 g, 7.1 mmol) in THF (10 mL), sodium hydride (284 mg, 7.1 mmol) was added. After 10 minutes, benzyl bromide (0.84 mL, 7.1 mmol) was added. The reaction mixture was stirred at reflux for 16 hours, then cooled to room temperature. The reaction mixture was partitioned between ethyl acetate and NaHCO₃(aq.). The organic layer was dried over MgSO₄, filtered and concentrated under reduced pressure and chromatography of the resulting liquid

on silica gel (hexane: ethyl acetate; 10:1) gave product (1.4 g, 85%). EI-MS m/z 232 (M+H)⁺.

c) Preparation of trans-2-benzyloxycyclohexylamine

- 5 To the solution of azide (350 mg, 1.51 mmol) in methanol (12 mL), dithiothreitol (0.76 mL, 7.55 mL) and trimethyl amine (0.63 mL, 4.53 mL) were added. The reaction mixture was stirred at room temperature for 16 hours. All solvent was evaporated. The residue was dissolved in ether (20 mL) and treated with ether/HCl. The organic layer was separated. The liquid layer was basified to pH= 7-8, then
10 extracted with ether (3x). The organic extracts were combined, dried over MgSO₄, filtered and concentrated under reduced pressure to give product (101 mg, 33%). EI-MS m/z 206 (M+H)⁺.

d) Preparation of trans-N-(2-benzyloxycyclohexyl)-N'-(2-tertbutyldimethylsilyl

- 15 oxy-4-nitrophenyl) urea

To a solution of 2-tert-butyldimethylsilyloxy-4-nitroaniline (200 mg, 0.74 mmol) in toluene, triethylamine (0.13 ml, 0.89 mmol) and triphosgene (88.4 mg, 0.3 mmol) were added. The reaction mixture was stirred at 80 °C for 3 hours. It was cooled to room temperature and all solvent was evaporated. Trans-2-
20 benzyloxycyclohexylamine (101mg, 0.49 mmol) in DMF (1 mL) was added to the residue. The reaction mixture was stirred at 80°C for 16 hours, and cooled to room temperature. Chromatography of the resulting liquid on silica gel (hexane : ethyl acetate; 5:1) gave product (100 mg, 41%). EI-MS m/z 500 (M+H)⁺.

- 25 e) Preparation of trans-N-(2-Benzyloxycyclohexyl)-N'-(2-hydroxy-4-nitrophenyl)urea

To a solution of trans-N-(2-Benzyloxycyclohexyl)-N'-(2-tert-butyldimethylsilyloxy-4-nitrophenyl) urea (100 mg, 0.2 mmol) in acetonitrile(2 mL), triethylamine hydrofluoride (0.1 mL, 0.6 mmol) was added. The reaction mixture
30 was stirred at room temperature for 30 minutes. The reaction mixture was partitioned between ethyl acetate and water. The organic layer was dried over MgSO₄, filtered and concentrated under reduced pressure to give product (73 mg, 95%). EI-MS m/z 386 (M+H)⁺.

Using analagous methods to those described above, the following compounds have been prepared:

5 Example 3: N-trans-(2-Hydroxycyclohexyl)-N'-(2-hydroxy-4-nitrophenyl)urea mp 144.6-145.2 C

Example 4: N-trans-(2-Benzoxycyclopentyl)-N'-(2-hydroxy-4-nitrophenyl)urea mp 53.4-54.4 C

10 Example 5: N-trans-(2-Methoxycyclohexyl)-N'-(2-hydroxy-4-nitrophenyl)urea mp 88.8-89.6 C

Example 6: N-(1,1-Dimethyl-2-benzoxylethyl)-N'-(2-hydroxy-4-nitrophenyl)urea m.p: 111.9-112.3°C

15

Example 7

Preparation of N-Allyl-N'-(2-hydroxy-4-nitrophenyl)urea

To a solution of allyl isocyanate (400 mg, 4.03 mmol) in toluene, the 2-amino-5-nitrophenol (621 mg, 4.03 mmol) was added. The reaction mixture was stirred at 80 °C for 24 hours, then cooled to room temperature. The product was purified by precipitation from toluene and filtering (644 mg, 67 %). m.p: 135-136.4°C; EI-MS m/z 238 (M+H)⁺.

20

Example 8

Preparation of N-t-Butyl-N'-(2-hydroxy-4-nitrophenyl)urea

To a solution of t-butyl isocyanate (400 mg, 4.04 mmol) in toluene, the 2-amino-5-nitrophenol (622 mg, 4.04 mmol) was added. The reaction mixture was stirred at 80°C for 24 hours, then cooled to room temperature. The product was purified by precipitation from toluene and filtering (864 mg, 85 %). m.p: 99.0-101.1°C; EI-MS m/z 254 (M+H)⁺.

30

Example 9

Preparation of N-[2-(Ethoxycarbonyl)ethyl]-N'-(2-hydroxy-4-nitrophenyl)urea

To a solution of ethyl 2-isocyanate propionate (372 mg, 2.6 mmol) in toluene, the 2-amino-5-nitrophenol (400 mg, 2.6 mmol) was added. The reaction mixture was stirred at 80°C for 24 hours, then cooled to room temperature. The

35

product was purified by precipitation from toluene and filtering (678 mg, 88 %).
m.p: 114.6-115.8°C; EI-MS m/z 298 (M+H)⁺.

Example 10

5 Preparation of N-Isopropyl-N'-(2-hydroxy-4-nitrophenyl)urea

To a solution of isopropyl isocyanate (221 mg, 2.6 mmol) in toluene, 2-amino-5-nitrophenol (400 mg, 2.6 mmol) was added. The reaction mixture was stirred at 80°C for 24 hours, then cooled to room temperature. The product was purified by precipitation from toluene and filtering (570 mg, 92 %). m.p: 159.8-
10 161.4°C; EI-MS m/z 240 (M+H)⁺.

Example 11

Preparation of N-(2-Hydroxy-4-nitrophenyl)-N'-(dimethylacetal)urea

To a solution of 2-*tert*-butyldimethylsilyloxy-4-nitroaniline (200 mg, 0.75 mmol) in
15 toluene (5 mL), triphosgene (84 mg, 0.3 mmol) and triethylamine (0.13 mL, 0.9 mmol) were added. The reaction mixture was stirred at 80°C for 3 hours, Then it was cooled to room temperature and all solvent was evaporated. The residue was dissolved in DMF (1 mL) and aminoacetaldehyde dimethylacetal (0.08 mL, 0.75 mmol) was added. The reaction mixture was stirred at 80°C for 16 hours
20 Chromatography of the resulting liquid on silica gel (50%Ethyl acetate/Hexane) gave desired product (117 mg, 55 %). EI-MS m/z 286.2 (M⁺).mp: 168.3-169.0°C.

Example 12

Preparation of N-(2-Hydroxy-4-nitrophenyl)-N'-(2-methoxyethyl)urca

25 To a solution of 2-*tert*-butyldimethylsilyloxy-4-nitroaniline (200 mg, 0.75 mmol) in toluene (5 mL), triphosgene (84 mg, 0.3 mmol) and triethylamine (0.13 mL, 0.9 mmol) were added. The reaction mixture was stirred at 80°C for 3 hours. Then it was cooled to room temperature and all solvent was evaporated. The residue was dissolved in DMF (1 mL) and 2-methoxyethylamine (56.3 mg, 0.75 mmol) was
30 added. The reaction mixture was stirred at 80°C for 16 hours. Chromatography of the resulting liquid on silica gel (50%Ethyl acetate/Hexane) gave desired product (95 mg, 50 %). EI-MS m/z 256.2 (M⁺). mp: 190.0-190.7°C.

Example 13

35 Preparation of N-(2-Hydroxy-4-nitrophenyl)-N'-(2-benzyloxypropyl)urea

- To a solution of 2-*tert*-butyldimethylsilyloxy-4-nitroaniline (300 mg, 1.125 mmol) in toluene (10 mL), triphosgene (126 mg, 0.45 mmol) and triethylamine (0.195 mL, 1.35 mmol) were added. The reaction mixture was stirred at 80°C for 3 hours. Then it was cooled to room temperature and all solvent was evaporated. The residue was dissolved in DMF (1 mL) and 2-benzyloxypropylamine (185.6 mg, 1.125 mmol) was added. The reaction mixture was stirred at 80°C for 16 hours. Chromatography of the resulting liquid on silica gel (50% Ethyl acetate/Hexane) gave desired product (160 mg, 41 %). EI-MS *m/z* 346.4 (*M*⁺). mp: 64.6-65.2°C.

10

Example 14

Preparation of N-(2-Hydroxy-4-nitrophenyl)-N'-(2-methoxyisopropyl)urea

- To a solution of 2-*tert*-butyldimethylsilyloxy-4-nitroaniline (200 mg, 0.75 mmol) in toluene (5 mL), triphosgene (84 mg, 0.3 mmol) and triethylamine (0.13 mL, 0.9 mmol) were added. The reaction mixture was stirred at 80°C for 3 hours. Then it was cooled to room temperature and all solvent was evaporated. The residue was dissolved in DMF (1 mL) and 2-methoxyisopropylamine (66.8 mg, 0.75 mmol) was added. The reaction mixture was stirred at 80°C for 16 hours. Chromatography of the resulting liquid on silica gel (50% Ethyl acetate/Hexane) gave desired product (80 mg, 40 %). EI-MS *m/z* 270.2 (*M*⁺). mp: 170.9-171.5°C.

20

Example 15

Preparation of N-(2-Hydroxy-4-nitrophenyl)-N'-(1-carbonyl-2-methylpropyl)urea

- a) Preparation of N-(2-Hydroxy-4-nitrophenyl)-N'-(1-(ethoxycarbonyl)-2-methylpropyl)urea
- To a solution of ethyl 2-isocyanato-3-methylbutyrate (333 mg, 1.95 mmol) in DMF (1.0 mL), 2-hydroxy-4-nitroaniline (300 mg, 1.95 mmol) was added. The reaction mixture was stirred at 80°C for 16 hours. Chromatography of the resulting liquid on silica gel gave desired product (420 mg, 66%). EI-MS *m/z* 326 (*M*⁺).
- b) Preparation of N-(2-Hydroxy-4-nitrophenyl)-N'-(1-carbonyl-2-methylpropyl)urea
- To a solution of N-(2-Hydroxy-4-nitrophenyl)-N'-(1-(ethoxycarbonyl)-2-methylpropyl)urea (200 mg, 0.62 mmol) in ethanol/water (10 mL/1 mL), sodium hydroxide (123 mg, 3.1 mmol) was added. The reaction mixture was stirred at reflux temperature for 16 hours. Then the reaction mixture was cooled to room temperature and all the solvent was evaporated. 3N of HCl was added to pH = 1. A yellow solid precipitated, it was filtered to give desired product (86 mg, 47 %). EI-MS *m/z* 298.3 (*M*⁺). mp: 168.4 -169.2°C.

Example 16

Preparation of N-(2-Hydroxy-4-nitrophenyl)-N'-(1,2-dimethyl-2-benzoxypethyl)-urea

a) Preparation of 1-methyl-2-hydroxypropylazide

5 To a solution of cis-2,3-epoxybutane (2 g, 27.74 mmol) in methanol/water (83 mL/8 mL), sodium azide (2.7 g, 41.61 mmol) and ammonium chloride (2.97 g, 55.48 mmol) were added. The reaction mixture was stirred at reflux temperature for 16 hours. Then cooled to room temperature and evaporated all solvent. The residue was extracted with ethyl acetate (3x). The combined organic phase was dried over MgSO_4 , filtered
10 and concentrated under reduced pressure to give desired product (2.6 g, 82%). EI-MS m/z 88 (M^+-N_2).

b) Preparation of 1-methyl-2-benzoxypylazide

To a solution of 1-methyl-2-hydroxypropylazide (700 mg, 6.09 mmol) in THF (10 mL), sodium hydride (60 %, 243 mg, 6.09 mmol) was added. After 10 min, The
15 benzyl bromide (0.72 mL, 6.09 mmol) was added. The reaction mixture was stirred at reflux temperature for 16 hours. Then the reaction mixture was partitioned between ethyl acetate and $\text{NaHCO}_3(\text{aq})$. The organic layer is dried over MgSO_4 and filtered. The solvent was evaporated and chromatography of the resulting solid on silica gel gave the desired product (950 mg, 76 %). EI-MS m/z 178 (M^+-N_2).

20 c) Preparation of 1-methyl-2-benzoxypylamine

To a solution of 1-methyl-2-benzoxypylazide (300 mL, 1.46 mmol) in ether (10 mL), lithium aluminum hydride (167 mg, 4.38 mmol) was added. The reaction mixture was stirred at room temperature for 1 hours. Then 0.17 mL of H_2O , 0.2 mL of 15% NaOH and 0.42 mL of H_2O were added. The solid was filtered. The liquid
25 was concentrated under reduced pressure to give desired product (240 mg, 92 %). EI-MS m/z 180 (M^+).

d) Preparation of N-(2-Hydroxy-4-nitrophenyl)-N'-(1,2-dimethyl-2-benzoxypethyl)urea

To a solution of 2-*tert*-butyldimethylsilyloxy-4-nitroaniline (300 mg, 1.125 mmol) in toluene (10 mL), triphosgene (126 mg, 0.45 mmol) and triethylamine (0.195 mL, 1.35
30 mmol) were added. The reaction mixture was stirred at 80°C for 3 hours, Then was cooled to room temperature and evaporated all solvent. The residue was dissolved in DMF (1 mL). 1-methyl-2-benzoxypylamine (200 mg, 1.12 mmol) was added. The reaction mixture was stirred at 80°C for 16 hours Chromatography of the resulting liquid on silica gel gave desired product (235 mg, 59 %). EI-MS m/z 360.4 (M^+).

35

Example 17Preparation of N-(2-benzenesulfonylamino-4-cyanophenyl)-N'-(isopropyl)urea

a) Preparation of 3,4 diamino benzonitrile

- 5 4-Amino 3-nitro-benzonitrile(5.0g, 0.03 moles) was dissolved in ethyl acetate then treated with 2.5 g of 10% Pd/C. The reaction mixture was flushed with hydrogen and allowed to stir overnight at 23 °C. The reaction was not quite complete so 0.5 g more 10% Pd/C was added. After 2 hours the reaction was complete. The solution was filtered through celite, concentrated and used without further purification(4.67 g).

b) Preparation of benzenesulfonylamino-4-cyanoaniline

- 10 A solution of 3,4 diamino benzonitrile(10.7 g, 0.08 mol) in methylene chloride was treated with phenyl sulfonyl chloride (2 eq, 0.16 mol) and triethyl amine (2 eq, 0.16 mol) for 18 hours at 23 °C. The reaction mixture was partitioned between water and methylene chloride. The organic layer was separated and dried over sodium sulfate. The solution was filtered and concentrated to 50 mL and a solid was precipitated out
15 with hexanes. This solid was dissolved in tetrahydrofuran and treated with 25% NaOMe in methanol. The reaction was complete after 5 minutes. The reaction mixture was acidified to pH 7 with ammonium chloride solution, then it was extracted with methylene chloride. The organic layer was dried over magnesium sulfate, filtered and concentrated to 50 mL. Hexanes were added to precipitate desired as a
20 white solid(19.7 grams).

- c) Preparation of N-(2-benzenesulfonylamino-4-cyanophenyl)-N'-(isopropyl)urea To a solution of isopropylisocyanate (31.2 mg, 0.37 mmol) in DMF (0.5 ml), 2-benzenesulfonylamino-4-cyanoaniline (100 mg, 0.37 mmol) was added. The reaction mixture was stirred at 80°C for 3 hours. Chromatography of the resulting liquid on
25 silica gel gave the desired product (85 mg, 65%). EI-MS m/z 359.4 (M⁺).

METHOD OF TREATMENT

The compounds of Formula (I) and (II), or a pharmaceutically acceptable salt thereof can be used in the manufacture of a medicament for the prophylactic or therapeutic treatment of any disease state in a human, or other mammal, which is
5 exacerbated or caused by excessive or unregulated IL-8 cytokine production by such mammal's cell, such as but not limited to monocytes and/or macrophages, or other chemokines which bind to the IL-8 a or b receptor, also referred to as the type I or type II receptor.

Accordingly, the present invention provides a method of treating a
10 chemokine mediated disease, wherein the chemokine is one which binds to an IL-8 a or b receptor and which method comprises administering an effective amount of a compound of Formula (I), or (II) or a pharmaceutically acceptable salt thereof. In particular, the chemokines are treating IL-8, GRO α , GRO β , GRO γ , NAP-2 and ENA-78.

15 For purposes of simplicity, compounds of Formula (I) and (II) will be referred to as compounds of Formula (I).

The compounds of Formula (I) are administered in an amount sufficient to inhibit cytokine function, in particular treating IL-8, GRO α , GRO β , GRO γ , NAP-2 and ENA-78, such that they are biologically regulated down to normal levels of
20 physiological function, or in some case to subnormal levels, so as to ameliorate the disease state. Abnormal levels of treating IL-8, GRO α , GRO β , GRO γ , NAP-2 and ENA-78 for instance in the context of the present invention, constitute: (i) levels of free IL-8 greater than or equal to 1 picogram per mL; (ii) any cell treating IL-8, GRO α , GRO β , GRO γ , NAP-2 and ENA-78 above normal physiological levels; or
25 (iii) the presence treating IL-8, GRO α , GRO β , GRO γ , NAP-2 and ENA-78 above basal levels in cells or tissues in which treating IL-8, GRO α , GRO β , GRO γ , NAP-2 and ENA-78 respectively, is produced.

There are many disease states in which excessive or unregulated IL-8 production is implicated in exacerbating and/or causing the disease. Chemokine
30 mediated diseases include psoriasis, atopic dermatitis, arthritis, asthma, chronic obstructive pulmonary disease, adult respiratory distress syndrome, inflammatory bowel disease, Crohn's disease, ulcerative colitis, stroke, septic shock, endotoxic shock, gram negative sepsis, toxic shock syndrome, cardiac and renal reperfusion injury, glomerulonephritis, thrombosis, graft vs. host reaction, alzheimers disease,
35 allograft rejections, malaria, restinosis, angiogenesis or undesired hematopoietic stem cells release.

These diseases are primarily characterized by massive neutrophil infiltration, T-cell infiltration, or neovascular growth, and are associated with increased IL-8, GRO α , GRO β , GRO γ or NAP-2 production which is responsible for the chemotaxis of neutrophils into the inflammatory site or the directional growth of endothelial cells. In contrast to other inflammatory cytokines (IL-1, TNF, and IL-6), IL-8, GRO α , GRO β , GRO γ or NAP-2 has the unique property of promoting neutrophil chemotaxis, enzyme release including but not limited to elastase release as well as superoxide production and activation. The α -chemokines but particularly GRO α , GRO β , GRO γ or NAP-2, working through the IL-8 type I or II receptor can promote the neovascularization of tumors by promoting the directional growth of endothelial cells. Therefore, the inhibition of IL-8 induced chemotaxis or activation would lead to a direct reduction in the neutrophil infiltration.

Recent evidence also implicates the role of chemokines in the treatment of HIV infections, Littleman et al., Nature 381, pp.661 (1996) and Koup et al., Nature 381, pp. 667 (1996).

The present invention also provides for a means of treating, in an acute setting, as well as preventing, in those individuals deemed susceptible to, CNS injuries by the chemokine receptor antagonist compounds of Formula (I).

CNS injuries as defined herein include both open or penetrating head trauma, such as by surgery, or a closed head trauma injury, such as by an injury to the head region. Also included within this definition is ischemic stroke, particularly to the brain area.

Ischemic stroke may be defined as a focal neurologic disorder that results from insufficient blood supply to a particular brain area, usually as a consequence of an embolus, thrombi, or local atheromatous closure of the blood vessel. The role of inflammatory cytokines in this area has been emerging and the present invention provides a mean for the potential treatment of these injuries. Relatively little treatment, for an acute injury such as these has been available.

TNF- α is a cytokine with proinflammatory actions, including endothelial leukocyte adhesion molecule expression. Leukocytes infiltrate into ischemic brain lesions and hence compounds which inhibit or decrease levels of TNF would be useful for treatment of ischemic brain injury. See Liu et al., Stroke, Vol. 25., No. 7, pp 1481-88 (1994) whose disclosure is incorporated herein by reference.

Models of closed head injuries and treatment with mixed 5-LO/CO agents is discussed in Shohami et al., J. of Vasc & Clinical Physiology and Pharmacology, Vol. 3, No. 2, pp. 99-107 (1992) whose disclosure is incorporated herein by

reference. Treatment which reduced edema formation was found to improve functional outcome in those animals treated.

The compounds of Formula (I) are administered in an amount sufficient to
5 inhibit IL-8, binding to the IL-8 alpha or beta receptors, from binding to these
receptors, such as evidenced by a reduction in neutrophil chemotaxis and activation.
The discovery that the compounds of Formula (I) are inhibitors of IL-8 binding is
based upon the effects of the compounds of Formulas (I) in the *in vitro* receptor
binding assays which are described herein. The compounds of Formula (I) have
10 been shown, in some instances, to be dual inhibitors of both recombinant type I and
type II IL-8 receptors. Preferably the compounds are inhibitors of only one
receptor, more preferably Type II.

As used herein, the term "IL-8 mediated disease or disease state" refers to
15 any and all disease states in which treating IL-8, GRO α , GRO β , GRO γ , NAP-2 and
ENA-78 plays a role, either by production of IL-8, GRO α , GRO β , GRO γ , NAP-2 or
ENA-78 themselves, or by IL-8, GRO α , GRO β , GRO γ , NAP-2 or ENA-78 causing
another monokine to be released, such as but not limited to IL-1, IL-6 or TNF. A
disease state in which, for instance, IL-1 is a major component, and whose
20 production or action, is exacerbated or secreted in response to IL-8, would therefore
be considered a disease stated mediated by IL-8.

As used herein, the term "chemokine mediated disease or disease state" refers
to any and all disease states in which a chemokine which binds to an IL-8 a or b
25 receptor plays a role, such as but not limited to IL-8, GRO α , GRO β , GRO γ , NAP-2
or ENA-78. This would include a disease state in which, IL-8 plays a role, either by
production of IL-8 itself, or by IL-8 causing another monokine to be released, such as
but not limited to IL-1, IL-6 or TNF. A disease state in which, for instance, IL-1 is a
major component, and whose production or action, is exacerbated or secreted in
30 response to IL-8, would therefore be considered a disease stated mediated by IL-8.

As used herein, the term "cytokine" refers to any secreted polypeptide that
affects the functions of cells and is a molecule which modulates interactions
between cells in the immune, inflammatory or hematopoietic response. A cytokine
35 includes, but is not limited to, monokines and lymphokines, regardless of which
cells produce them. For instance, a monokine is generally referred to as being

produced and secreted by a mononuclear cell, such as a macrophage and/or monocyte. Many other cells however also produce monokines, such as natural killer cells, fibroblasts, basophils, neutrophils, endothelial cells, brain astrocytes, bone marrow stromal cells, epidermal keratinocytes and B-lymphocytes. Lymphokines are generally referred to as being produced by lymphocyte cells. Examples of cytokines include, but are not limited to, Interleukin-1 (IL-1), Interleukin-6 (IL-6), Interleukin-8 (IL-8), Tumor Necrosis Factor-alpha (TNF- α) and Tumor Necrosis Factor beta (TNF- β).

As used herein, the term "chemokine" refers to any secreted polypeptide that affects the functions of cells and is a molecule which modulates interactions between cells in the immune, inflammatory or hematopoietic response, similar to the term "cytokine" above. A chemokine is primarily secreted through cell transmembranes and causes chemotaxis and activation of specific white blood cells and leukocytes, neutrophils, monocytes, macrophages, T-cells, B-cells, endothelial cells and smooth muscle cells. Examples of chemokines include, but are not limited to, IL-8, GRO- α , GRO- β , GRO- γ , NAP-2, ENA-78, IP-10, MIP-1a, MIP-b, PF4, and MCP 1, 2, and 3.

In order to use a compound of Formula (I) or a pharmaceutically acceptable salt thereof in therapy, it will normally be formulated into a pharmaceutical composition in accordance with standard pharmaceutical practice. This invention, therefore, also relates to a pharmaceutical composition comprising an effective, non-toxic amount of a compound of Formula (I) and a pharmaceutically acceptable carrier or diluent.

Compounds of Formula (I), pharmaceutically acceptable salts thereof and pharmaceutical compositions incorporating such may conveniently be administered by any of the routes conventionally used for drug administration, for instance, orally, topically, parenterally or by inhalation. The compounds of Formula (I) may be administered in conventional dosage forms prepared by combining a compound of Formula (I) with standard pharmaceutical carriers according to conventional procedures. The compounds of Formula (I) may also be administered in conventional dosages in combination with a known, second therapeutically active compound. These procedures may involve mixing, granulating and compressing or dissolving the ingredients as appropriate to the desired preparation. It will be

appreciated that the form and character of the pharmaceutically acceptable character or diluent is dictated by the amount of active ingredient with which it is to be combined, the route of administration and other well-known variables. The carrier(s) must be "acceptable" in the sense of being compatible with the other ingredients of the formulation and not deleterious to the recipient thereof.

The pharmaceutical carrier employed may be, for example, either a solid or liquid. Exemplary of solid carriers are lactose, terra alba, sucrose, talc, gelatin, agar, pectin, acacia, magnesium stearate, stearic acid and the like. Exemplary of liquid carriers are syrup, peanut oil, olive oil, water and the like. Similarly, the carrier or diluent may include time delay material well known to the art, such as glyceryl mono-stearate or glyceryl distearate alone or with a wax.

A wide variety of pharmaceutical forms can be employed. Thus, if a solid carrier is used, the preparation can be tableted, placed in a hard gelatin capsule in powder or pellet form or in the form of a troche or lozenge. The amount of solid carrier will vary widely but preferably will be from about 25mg. to about 1g. When a liquid carrier is used, the preparation will be in the form of a syrup, emulsion, soft gelatin capsule, sterile injectable liquid such as an ampule or nonaqueous liquid suspension.

Compounds of Formula (I) may be administered topically, that is by non-systemic administration. This includes the application of a compound of Formula (I) externally to the epidermis or the buccal cavity and the instillation of such a compound into the ear, eye and nose, such that the compound does not significantly enter the blood stream. In contrast, systemic administration refers to oral, intravenous, intraperitoneal and intramuscular administration.

Formulations suitable for topical administration include liquid or semi-liquid preparations suitable for penetration through the skin to the site of inflammation such as liniments, lotions, creams, ointments or pastes, and drops suitable for administration to the eye, ear or nose. The active ingredient may comprise, for topical administration, from 0.001% to 10% w/w, for instance from 1% to 2% by weight of the Formulation. It may however comprise as much as 10% w/w but preferably will comprise less than 5% w/w, more preferably from 0.1% to 1% w/w of the Formulation.

Lotions according to the present invention include those suitable for application to the skin or eye. An eye lotion may comprise a sterile aqueous solution optionally containing a bactericide and may be prepared by methods similar to those for the preparation of drops. Lotions or liniments for application to the skin may also include an agent to hasten drying and to cool the skin, such as an alcohol or acetone, and/or a moisturizer such as glycerol or an oil such as castor oil or arachis oil.

10 Creams, ointments or pastes according to the present invention are semi-solid formulations of the active ingredient for external application. They may be made by mixing the active ingredient in finely-divided or powdered form, alone or in solution or suspension in an aqueous or non-aqueous fluid, with the aid of suitable machinery, with a greasy or non-greasy base. The base may comprise
15 hydrocarbons such as hard, soft or liquid paraffin, glycerol, beeswax, a metallic soap; a mucilage; an oil of natural origin such as almond, corn, arachis, castor or olive oil; wool fat or its derivatives or a fatty acid such as steric or oleic acid together with an alcohol such as propylene glycol or a macrogel. The formulation may incorporate any suitable surface active agent such as an anionic, cationic or
20 non-ionic surfactant such as a sorbitan ester or a polyoxyethylene derivative thereof. Suspending agents such as natural gums, cellulose derivatives or inorganic materials such as siliceous silicas, and other ingredients such as lanolin, may also be included.

25 Drops according to the present invention may comprise sterile aqueous or oily solutions or suspensions and may be prepared by dissolving the active ingredient in a suitable aqueous solution of a bactericidal and/or fungicidal agent and/or any other suitable preservative, and preferably including a surface active agent. The resulting solution may then be clarified by filtration, transferred to a
30 suitable container which is then sealed and sterilized by autoclaving or maintaining at 98-100 °C. for half an hour. Alternatively, the solution may be sterilized by filtration and transferred to the container by an aseptic technique. Examples of bactericidal and fungicidal agents suitable for inclusion in the drops are phenylmercuric nitrate or acetate (0.002%), benzalkonium chloride (0.01%) and
35 chlorhexidine acetate (0.01%). Suitable solvents for the preparation of an oily solution include glycerol, diluted alcohol and propylene glycol.

Compounds of Formula (I) may be administered parenterally, that is by intravenous, intramuscular, subcutaneous intranasal, intrarectal, intravaginal or intraperitoneal administration. The subcutaneous and intramuscular forms of parenteral administration are generally preferred. Appropriate dosage forms for such administration may be prepared by conventional techniques. Compounds of Formula (I) may also be administered by inhalation, that is by intranasal and oral inhalation administration. Appropriate dosage forms for such administration, such as an aerosol formulation or a metered dose inhaler, may be prepared by conventional techniques.

For all methods of use disclosed herein for the compounds of Formula (I), the daily oral dosage regimen will preferably be from about 0.01 to about 80 mg/kg of total body weight. The daily parenteral dosage regimen about 0.001 to about 80 mg/kg of total body weight. The daily topical dosage regimen will preferably be from 0.1 mg to 150 mg, administered one to four, preferably two or three times daily. The daily inhalation dosage regimen will preferably be from about 0.01 mg/kg to about 1 mg/kg per day. It will also be recognized by one of skill in the art that the optimal quantity and spacing of individual dosages of a compound of Formula (I) or a pharmaceutically acceptable salt thereof will be determined by the nature and extent of the condition being treated, the form, route and site of administration, and the particular patient being treated, and that such optimums can be determined by conventional techniques. It will also be appreciated by one of skill in the art that the optimal course of treatment, i.e., the number of doses of a compound of Formula (I) or a pharmaceutically acceptable salt thereof given per day for a defined number of days, can be ascertained by those skilled in the art using conventional course of treatment determination tests.

The invention will now be described by reference to the following biological examples which are merely illustrative and are not to be construed as a limitation of the scope of the present invention.

BIOLOGICAL EXAMPLES

The IL-8, and Gro- α chemokine inhibitory effects of compounds of the present invention were determined by the following *in vitro* assay:

Receptor Binding Assays:

[¹²⁵I] IL-8 (human recombinant) was obtained from Amersham Corp.,
Arlington Heights, IL, with specific activity 2000 Ci/mmol. Gro-a was obtained
from NEN- New England Nuclear. All other chemicals were of analytical grade.
High levels of recombinant human IL-8 type a and b receptors were individually
5 expressed in Chinese hamster ovary cells as described previously (Holmes, *et al.*,
Science, **1991**, 253, 1278). The Chinese hamster ovary membranes were
homogenized according to a previously described protocol (Haour, *et al.*, *J Biol*
Chem., 249 pp 2195-2205 (1974)). Except that the homogenization buffer was
10 changed to 10mM Tris-HCL, 1mM MgSO₄, 0.5mM EDTA (ethylene-diaminetetra-
acetic acid), 1mM PMSF (a-toluenesulphonyl fluoride), 0.5 mg/L Leupeptin, pH 7.5.
Membrane protein concentration was determined using Pierce Co. micro-assay kit
using bovine serum albumin as a standard. All assays were performed in a 96-well
micro plate format. Each reaction mixture contained ¹²⁵I IL-8 (0.25 nM) or ¹²⁵I
Gro-a and 0.5 µg/mL of IL-8Ra or 1.0 µg/mL of IL-8Rb membranes in 20 mM Bis-
15 Trispropane and 0.4 mM Tris HCl buffers, pH 8.0, containing 1.2 mM MgSO₄, 0.1
mM EDTA, 25 mM NaCl and 0.03% CHAPS. In addition, drug or compound of
interest was added which had been pre-dissolved in DMSO so as to reach a final
concentration of between 0.01nM and 100 µM. The assay was initiated by addition
of ¹²⁵I-IL-8. After 1 hour at room temperature the plate was harvested using a
20 Tomtec 96-well harvester onto a glass fiber filtermat blocked with 1%
polyethylenimine/0.5% BSA and washed 3 times with 25 mM NaCl, 10 mM
TrisHCl, 1 mM MgSO₄, 0.5 mM EDTA, 0.03 % CHAPS, pH 7.4. The filter was
then dried and counted on the Betaplate liquid scintillation counter. The
recombinant IL-8 Ra, or Type I, receptor is also referred to herein as the non-
25 permissive receptor and the recombinant IL-8 Rb, or Type II, receptor is referred to
as the permissive receptor.

Exemplified compounds of Formula (I) noted herein in the Synthetic
Chemistry Section, as Examples 1 to 17, demonstrated an IC₅₀ from about 45 to
30 about <2 µg/mL in the permissive models for IL-8 receptor inhibition. The
compounds, N-trans-(2-benzyloxycyclohexyl)-N'-((2-benzenesulfonylamino)4-
cyanophenyl))urea; N-(ethylisopropylether)-N'-(2-hydroxy-4-nitro-phenyl)urea ; and
N-(2-carboxyethyl)-N'-(2-hydroxy-4-nitrophenyl)urca were found to be inactive in
this assay, as was the compound of Example 6.

35

Chemotaxis Assay:

The *in vitro* inhibitory properties of these compounds are determined in the neutrophil chemotaxis assay as described in Current Protocols in Immunology, vol I, Suppl 1, Unit 6.12.3., whose disclosure is incorporated herein by reference in its entirety. Neutrophils were isolated from human blood as described in Current Protocols in Immunology Vol I, Suppl 1 Unit 7.23.1, whose disclosure is incorporated herein by reference in its entirety. The chemoattractants IL-8, GRO- α , GRO- β , GRO- γ and NAP-2 are placed in the bottom chamber of a 48 multiwell chamber (Neuro Probe, Cabin John, MD) at a concentration between 0.1 and 100 nM. The two chambers are separated by a 5 μ m polycarbonate filter. When compounds of this invention are tested, they are mixed with the cells (0.001 - 1000 nM) just prior to the addition of the cells to the upper chamber. Incubation is allowed to proceed for between about 45 and 90 min at about 37°C in a humidified incubator with 5% CO₂. At the end of the incubation period, the polycarbonate membrane is removed and the top side washed, the membrane then stained using the Diff Quick staining protocol (Baxter Products, McGaw Park, IL, USA). Cells which have chemotaxed to the chemokine are visually counted using a microscope. Generally, four fields are counted for each sample, these numbers are averaged to give the average number of cells which had migrated. Each sample is tested in triplicate and each compound repeated at least four times. To certain cells (positive control cells) no compound is added, these cells represent the maximum chemotactic response of the cells. In the case where a negative control (unstimulated) is desired, no chemokine is added to the bottom chamber. The difference between the positive control and the negative control represents the chemotactic activity of the cells.

Elastase Release Assay:

The compounds of this invention are tested for their ability to prevent Elastase release from human neutrophils. Neutrophils are isolated from human blood as described in Current Protocols in Immunology Vol I, Suppl 1 Unit 7.23.1. PMNs 0.88×10^6 cells suspended in Ringer's Solution (NaCl 118, KCl 4.56, NaHCO₃ 25, KH₂PO₄ 1.03, Glucose 11.1, HEPES 5 mM, pH 7.4) are placed in each well of a 96 well plate in a volume of 50 μ l. To this plate is added the test compound (0.001 - 1000 nM) in a volume of 50 μ l, Cytochalasin B in a volume of 50 μ l (20 μ g/ml) and Ringers buffer in a volume of 50 μ l. These cells are allowed to warm (37 °C, 5% CO₂, 95% RH) for 5 min before IL-8, GRO α , GRO β , GRO γ or NAP-2 at a final concentration of 0.01 - 1000 nM was added. The reaction is

allowed to proceed for 45 min before the 96 well plate is centrifuged (800 xg 5 min) and 100 ul of the supernatant removed. This supernatant is added to a second 96 well plate followed by an artificial elastase substrate (MeOSuc-Ala-Ala-Pro-Val-AMC, Nova Biochem, La Jolla, CA) to a final concentration of 6 ug/ml dissolved in phosphate buffered saline. Immediately, the plate is placed in a fluorescent 96 well plate reader (Cytofluor 2350, Millipore, Bedford, MA) and data collected at 3 min intervals according to the method of Nakajima et al J. Biol Chem 254 4027 (1979). The amount of Elastase released from the PMNs is calculated by measuring the rate of MeOSuc-Ala-Ala-Pro-Val-AMC degradation.

TNF- α in Traumatic Brain Injury Assay

The present assay provides for examination of the expression of tumor necrosis factor mRNA in specific brain regions which follow experimentally induced lateral fluid-percussion traumatic brain injury (TBI) in rats. Adult Sprague-Dawley rats (n=42) were anesthetized with sodium pentobarbital (60 mg/kg, i.p.) and subjected to lateral fluid-percussion brain injury of moderate severity (2.4 atm.) centered over the left temporoparietal cortex (n=18), or "sham" treatment (anesthesia and surgery without injury, n=18). Animals are sacrificed by decapitation at 1, 6 and 24 hr. post injury, brains removed, and tissue samples of left (injured) parietal cortex (LC), corresponding area in the contralateral right cortex (RC), cortex adjacent to injured parietal cortex (LA), corresponding adjacent area in the right cortex (RA), left hippocampus (LH) and right hippocampus (RH) are prepared. Total RNA was isolated and Northern blot hybridization is performed and quantitated relative to an TNF- α positive control RNA (macrophage = 100%). A marked increase of TNF- α mRNA expression is observed in LH (104 \pm 17% of positive control, p < 0.05 compared with sham), LC (105 \pm 21%, p < 0.05) and LA (69 \pm 8%, p < 0.01) in the traumatized hemisphere 1 hr. following injury. An increased TNF- α mRNA expression is also observed in LH (46 \pm 8%, p < 0.05), LC (30 \pm 3%, p < 0.01) and LA (32 \pm 3%, p < 0.01) at 6 hr. which resolves by 24 hr. following injury. In the contralateral hemisphere, expression of TNF- α mRNA is increased in RH (46 \pm 2%, p < 0.01), RC (4 \pm 3%) and RA (22 \pm 8%) at 1 hr. and in RH (28 \pm 11%), RC (7 \pm 5%) and RA (26 \pm 6%, p < 0.05) at 6 hr. but not at 24 hr. following injury. In sham (surgery without injury) or naive animals, no consistent changes in expression of TNF- α mRNA are observed in any of the 6 brain areas in either hemisphere at any times. These results indicate that following parasagittal fluid-percussion brain injury, the temporal expression of TNF- α mRNA is altered in specific brain regions, including those of the non-traumatized hemisphere. Since TNF- α is able to induce nerve growth factor (NGF) and

stimulate the release of other cytokines from activated astrocytes, this post-traumatic alteration in gene expression of TNF- α plays an important role in both the acute and regenerative response to CNS trauma.

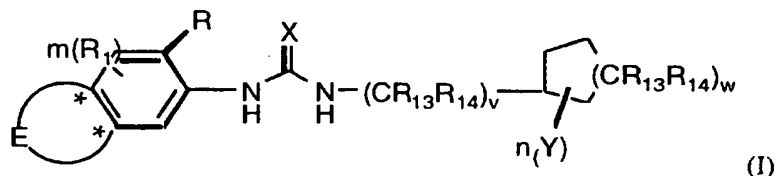
5 CNS Injury model for IL- β mRNA

 This assay characterizes the regional expression of interleukin-1 β (IL-1 β) mRNA in specific brain regions following experimental lateral fluid-percussion traumatic brain injury (TBI) in rats. Adult Sprague-Dawley rats (n=42) are anesthetized with sodium pentobarbital (60 mg/kg, i.p.) and subjected to lateral
10 fluid-percussion brain injury of moderate severity (2.4 atm.) centered over the left temporoparietal cortex (n=18), or "sham" treatment (anesthesia and surgery without injury). Animals are sacrificed at 1, 6 and 24 hr. post injury, brains removed, and tissue samples of left (injured) parietal cortex (LC), corresponding area in the contralateral right cortex (RC), cortex adjacent to injured parietal cortex (LA),
15 corresponding adjacent area in the right cortex (RA), left hippocampus (LH) and right hippocampus (RH) are prepared. Total RNA is isolated and Northern blot hybridization was performed and the quantity of brain tissue IL-1 β mRNA is presented as percent relative radioactivity of IL-1 β positive macrophage RNA which was loaded on same gel. At 1 hr. following brain injury, a marked and significant
20 increase in expression of IL-1 β mRNA is observed in LC ($20.0 \pm 0.7\%$ of positive control, n=6, $p < 0.05$ compared with sham animal), LH ($24.5 \pm 0.9\%$, $p < 0.05$) and LA ($21.5 \pm 3.1\%$, $p < 0.05$) in the injured hemisphere, which remained elevated up to 6 hr. post injury in the LC ($4.0 \pm 0.4\%$, n=6, $p < 0.05$) and LH ($5.0 \pm 1.3\%$, $p < 0.05$). In sham or naive animals, no expression of IL-1 β mRNA is observed in any of the
25 respective brain areas. These results indicate that following TBI, the temporal expression of IL-1 β mRNA is regionally stimulated in specific brain regions. These regional changes in cytokines, such as IL-1 β play a role in the post-traumatic.

 The above description fully discloses the invention including preferred
30 embodiments thereof. Modifications and improvements of the embodiments specifically disclosed herein are within the scope of the following claims. Without further elaboration, it is believed that one skilled in the art can, using the preceding description, utilize the present invention to its fullest extent. Therefore the Examples herein are to be construed as merely illustrative and not a limitation of the
35 scope of the present invention in any way. The embodiments of the invention in which an exclusive property or privilege is claimed are defined as follows.

What is Claimed Is:

1. A method of treating a chemokine mediated disease state, wherein the
 5 chemokine binds to an IL-8 a or b receptor in a mammal, which comprises
 administering to said mammal an effective amount of a compound of the formula:

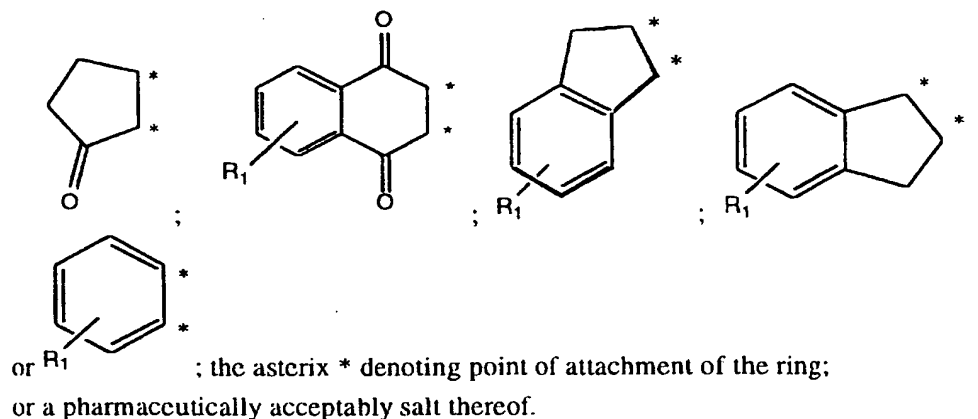


wherein

- 10 X is oxygen or sulfur;
 R is any functional moiety having an ionizable hydrogen and a pKa of 10 or less;
 R₁ is independently selected from hydrogen; halogen; nitro; cyano; halosubstituted
 C₁-10 alkyl; C₁-10 alkenyl; C₂-10 alkenyl; C₁-10 alkoxy; halosubstituted C₁-10
 alkoxy; azide; (CR₈R₈)_q S(O)_tR₄; hydroxy; hydroxy C₁-4alkyl; aryl; aryl C₁-4
 15 alkyl; aryloxy; aryl C₁-4 alkyloxy; heteroaryl; heteroarylalkyl; heterocyclic,
 heterocyclic C₁-4alkyl; heteroaryl C₁-4 alkyloxy; aryl C₂-10 alkenyl; heteroaryl
 C₂-10 alkenyl; heterocyclic C₂-10 alkenyl; (CR₈R₈)_qNR₄R₅; C₂-10 alkenyl
 C(O)NR₄R₅; (CR₈R₈)_q C(O)NR₄R₅; (CR₈R₈)_q C(O)NR₄R₁₀; S(O)₃H;
 S(O)₃R₈; (CR₈R₈)_q C(O)R₁₁; C₂-10 alkenyl C(O)R₁₁; C₂-10 alkenyl
 20 C(O)OR₁₁(CR₈R₈)_q C(O)OR₁₂; (CR₈R₈)_q OC(O) R₁₁;
 (CR₈R₈)_qNR₄C(O)R₁₁, (CR₈R₈)_q NHS(O)₂R₁₇, (CR₈R₈)_q S(O)₂NR₄R₅; or
 two R₁ moieties together may form O-(CH₂)₅O- or a 5 to 6 membered
 unsaturated ring;
 n is an integer having a value of 1 to 3;
 25 m is an integer having a value of 1 to 3;
 q is 0, or an integer having a value of 1 to 10;
 s is an integer having a value of 1 to 3;
 t is 0, or an integer having a value of 1 or 2;
 v is 0, or an integer having a value of 1 to 4;
 30 w is an integer having a value of 1 to 3;
 R₄ and R₅ are independently hydrogen, optionally substituted C₁-4 alkyl, optionally
 substituted aryl, optionally substituted aryl C₁-4alkyl, optionally substituted
 heteroaryl, optionally substituted heteroaryl C₁-4alkyl, heterocyclic,

heterocyclic C₁₋₄ alkyl, or R₄ and R₅ together with the nitrogen to which they are attached form a 5 to 7 member ring which may optionally comprise an additional heteroatom selected from oxygen, nitrogen, or sulfur;

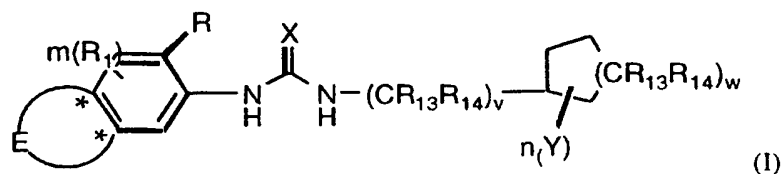
- Y is independently selected from hydrogen; halogen; nitro; cyano; halosubstituted C₁₋₁₀ alkyl; C₁₋₁₀ alkyl; C₂₋₁₀ alkenyl; C₁₋₁₀ alkoxy; halosubstituted C₁₋₁₀ alkoxy; azide; (CR₈R₈)_q S(O)_tR₄; hydroxy; hydroxyC₁₋₄alkyl; aryl; aryl C₁₋₄ alkyl; aryloxy; arylC₁₋₄ alkyloxy; heteroaryl; heteroarylalkyl; heteroaryl C₁₋₄ alkyloxy; heterocyclic, heterocyclic C₁₋₄alkyl; aryl C₂₋₁₀ alkenyl; heteroaryl C₂₋₁₀ alkenyl; heterocyclic C₂₋₁₀ alkenyl; (CR₈R₈)_q NR₄R₅; C₂₋₁₀ alkenyl C(O)NR₄R₅; (CR₈R₈)_q C(O)NR₄R₅; (CR₈R₈)_q C(O)NR₄R₁₀; S(O)₃H; S(O)₃R₈; (CR₈R₈)_q C(O)R₁₁; C₂₋₁₀ alkenyl C(O)R₁₁; C₂₋₁₀ alkenyl C(O)OR₁₁; C(O)R₁₁; (CR₈R₈)_q C(O)OR₁₂; (CR₈R₈)_q OC(O)R₁₁; (CR₈R₈)_q NR₄C(O)R₁₁, (CR₈R₈)_q NHS(O)₂R_d, (CR₈R₈)_q S(O)₂NR₄R₅; or two Y moieties together may form O-(CH₂)_sO- or a 5 to 6 membered unsaturated ring;
- R₆ and R₇ are independently hydrogen or a C₁₋₄ alkyl group, or R₆ and R₇ together with the nitrogen to which they are attached form a 5 to 7 member ring which ring may optionally contain an additional heteroatom which heteroatom is selected from oxygen, nitrogen or sulfur;
- R₈ is independently selected from hydrogen or C₁₋₄ alkyl;
- R₁₀ is C₁₋₁₀ alkyl C(O)₂R₈;
- R₁₁ is hydrogen, C₁₋₄ alkyl, optionally substituted aryl, optionally substituted aryl C₁₋₄alkyl, optionally substituted heteroaryl, optionally substituted heteroarylC₁₋₄alkyl, optionally substituted heterocyclic, or optionally substituted heterocyclicC₁₋₄alkyl;
- R₁₂ is hydrogen, C₁₋₁₀ alkyl, optionally substituted aryl or optionally substituted arylalkyl;
- R₁₃ and R₁₄ are independently hydrogen or C₁₋₄ alkyl;
- R₁₇ is C₁₋₄alkyl, aryl, arylalkyl, heteroaryl, heteroarylC₁₋₄alkyl, heterocyclic, or heterocyclicC₁₋₄alkyl, wherein the aryl, heteroaryl and heterocyclic rings may all be optionally substituted;
- R_d is NR₆R₇, alkyl, arylC₁₋₄alkyl, arylC₂₋₄ alkenyl, heteroaryl, heteroaryl-C₁₋₄alkyl, heteroarylC₂₋₄ alkenyl, heterocyclic, heterocyclicC₁₋₄ alkyl, wherein the aryl, heteroaryl and heterocyclic rings may all be optionally substituted;
- E is optionally selected from



2. The method according to Claim 1 wherein the ionizable hydrogen has a pKa of 3 to 10.
3. The method according to Claim 2 wherein R is hydroxy, carboxylic acid, thiol, SR_2 , OR_2 , $NH-C(O)R_a$, $C(O)NR_6R_7$, $NHS(O)_2R_b$, $S(O)_2NHR_c$, $NHC(X_2)NHR_b$, or tetrazolyl;
 - wherein R_2 is a substituted aryl, heteroaryl, or heterocyclic ring which ring contains the functional moiety providing an ionizable hydrogen having a pKa of 10 or less;
 - R_a is an alkyl, aryl, aryl C_{1-4} alkyl, heteroaryl, heteroaryl C_{1-4} alkyl, heterocyclic, or a heterocyclic C_{1-4} alkyl moiety, all of which may be optionally substituted;
 - R_b is a NR_6R_7 , alkyl, aryl, aryl C_{1-4} alkyl, aryl C_{2-4} alkenyl, heteroaryl, heteroaryl C_{1-4} alkyl, heteroaryl C_{2-4} alkenyl, heterocyclic, heterocyclic C_{1-4} alkyl, heterocyclic C_{2-4} alkenyl moiety, camphor, all of which may be optionally substituted one to three times independently by halogen; nitro; halosubstituted C_{1-4} alkyl; C_{1-4} alkyl; C_{1-4} alkoxy; $NR_9C(O)R_a$; $C(O)NR_6R_7$, $S(O)_3H$, or $C(O)OC_{1-4}$ alkyl;
 - R_9 is hydrogen or a C_{1-4} alkyl;
 - R_c is alkyl, aryl, aryl C_{1-4} alkyl, aryl C_{2-4} alkenyl, heteroaryl, heteroaryl C_{1-4} alkyl, heteroaryl C_{2-4} alkenyl, heterocyclic, heterocyclic C_{1-4} alkyl, or a heterocyclic C_{2-4} alkenyl moiety, all of which may be optionally substituted one to three times independently by halogen, nitro, halosubstituted C_{1-4} alkyl, C_{1-4} alkyl, C_{1-4} alkoxy, $NR_9C(O)R_a$, $C(O)NR_6R_7$, $S(O)_3H$, or $C(O)OC_{1-4}$ alkyl; and

X₂ is oxygen or sulfur.

4. The method according to Claim 3 wherein the R₂ is optionally substituted one to three times by halogen, nitro, halosubstituted C₁₋₁₀ alkyl, C₁₋₁₀ alkyl, C₁₋₁₀ alkoxy, hydroxy, SH, C(O)NR₆R₇, NH-C(O)R_a, NHS(O)R_b, S(O)NR₆R₇, C(O)OR₈, or a tetrazolyl ring.
5. The method according to Claim 3 wherein R is OH, -NHS(O)₂R_b or C(O)OH.
6. The method according to Claim 1 wherein R₁ is halogen, cyano, nitro, CF₃, C(O)NR₄R₅, alkenyl C(O)NR₄R₅, C(O)R₄R₁₀, alkenyl C(O)OR₁₂, heteroaryl, heteroarylalkyl, heteroaryl alkenyl, or S(O)NR₄R₅.
7. The method according to Claim 1 wherein Y is halogen, C₁₋₄ alkoxy, optionally substituted aryl, optionally substituted arylalkoxy, methylene dioxy, NR₄R₅, thioC₁₋₄alkyl, thioaryl, halosubstituted alkoxy, optionally substituted C₁₋₄alkyl, hydroxy alkyl.
8. The method according to Claim 1 wherein R is OH, SH, or NHS(O)₂R_b and R₁ is substituted in the 3-position, the 4- position or di substituted in the 3,4- position by an electron withdrawing moiety.
9. The method according to any of Claims 1 to 8 wherein the mammal is afflicted with a chemokine mediated disease selected from psoriasis, or atopic dermatitis, asthma, chronic obstructive pulmonary disease, adult respiratory distress syndrome, arthritis, inflammatory bowel disease, Crohn's disease, ulcerative colitis, septic shock, endotoxic shock, gram negative sepsis, toxic shock syndrome, stroke, cardiac and renal reperfusion injury, glomerulo-nephritis, thrombosis, neurotrauma, alzheimers disease, graft vs. host reaction, or allograft rejections.
10. A compound of the formula:



wherein

X is oxygen or sulfur;

R is any functional moiety having an ionizable hydrogen and a pKa of 10 or less;

- 5 R₁ is independently selected from hydrogen; halogen; nitro; cyano; halosubstituted C₁₋₁₀ alkyl; C₁₋₁₀ alkyl; C₂₋₁₀ alkenyl; C₁₋₁₀ alkoxy; halosubstituted C₁₋₁₀ alkoxy; azide; (CR₈R₈)_q S(O)_tR₄; hydroxy; hydroxy C₁₋₄alkyl; aryl; aryl C₁₋₄ alkyl; aryloxy; aryl C₁₋₄ alkyloxy; heteroaryl; heteroarylalkyl; heterocyclic, heterocyclic C₁₋₄alkyl; heteroaryl C₁₋₄ alkyloxy; aryl C₂₋₁₀ alkenyl; heteroaryl
- 10 C₂₋₁₀ alkenyl; heterocyclic C₂₋₁₀ alkenyl; (CR₈R₈)_qNR₄R₅; C₂₋₁₀ alkenyl C(O)NR₄R₅; (CR₈R₈)_q C(O)NR₄R₅; (CR₈R₈)_q C(O)NR₄R₁₀; S(O)₃H; S(O)₃R₈; (CR₈R₈)_q C(O)R₁₁; C₂₋₁₀ alkenyl C(O)R₁₁; C₂₋₁₀ alkenyl C(O)OR₁₁; (CR₈R₈)_q C(O)OR₁₂; (CR₈R₈)_q OC(O) R₁₁; (CR₈R₈)_qNR₄C(O)R₁₁; (CR₈R₈)_q NHS(O)₂R₁₇; (CR₈R₈)_q S(O)₂NR₄R₅; or
- 15 two R₁ moieties together may form O-(CH₂)₅O- or a 5 to 6 membered unsaturated ring;

n is an integer having a value of 1 to 3;

m is an integer having a value of 1 to 3;

q is 0, or an integer having a value of 1 to 10;

- 20 s is an integer having a value of 1 to 3;

t is 0, or an integer having a value of 1 or 2;

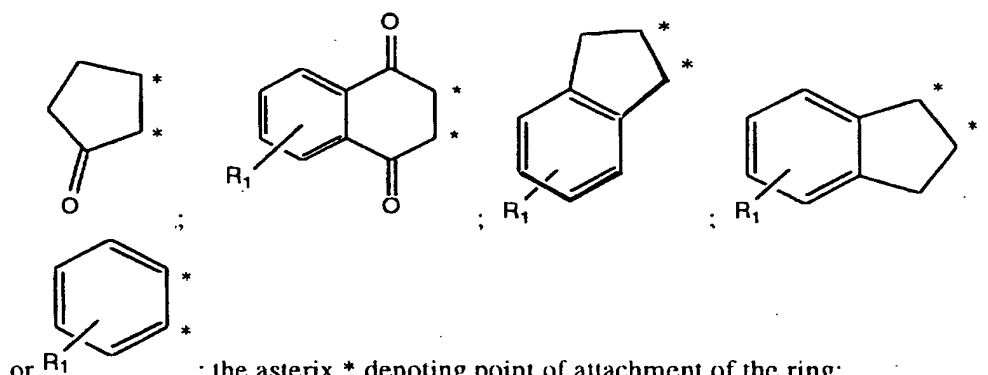
v is 0, or an integer having a value of 1 to 4;

w is an integer having a value of 1 to 3;

- 25 R₄ and R₅ are independently hydrogen, optionally substituted C₁₋₄ alkyl, optionally substituted aryl, optionally substituted aryl C₁₋₄alkyl, optionally substituted heteroaryl, optionally substituted heteroaryl C₁₋₄alkyl, heterocyclic, heterocyclic C₁₋₄ alkyl, or R₄ and R₅ together with the nitrogen to which they are attached form a 5 to 7 member ring which may optionally comprise an additional heteroatom selected from oxygen, nitrogen, or sulfur;

- 30 Y is independently selected from hydrogen; halogen; nitro; cyano; halosubstituted C₁₋₁₀ alkyl; C₁₋₁₀ alkyl; C₂₋₁₀ alkenyl; C₁₋₁₀ alkoxy; halosubstituted C₁₋₁₀ alkoxy; azide; (CR₈R₈)_q S(O)_tR₄; hydroxy; hydroxyC₁₋₄alkyl; aryl; aryl C₁₋₄ alkyl; aryloxy; arylC₁₋₄ alkyloxy; heteroaryl; heteroarylalkyl; heteroaryl C₁₋₄

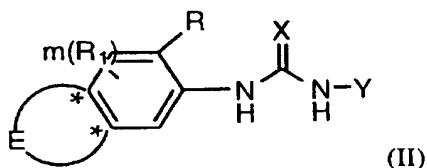
- alkyloxy; heterocyclic, heterocyclic C₁₋₄alkyl; aryl C₂₋₁₀ alkenyl; heteroaryl C₂₋₁₀ alkenyl; heterocyclic C₂₋₁₀ alkenyl; (CR₈R₈)_q NR₄R₅; C₂₋₁₀ alkenyl C(O)NR₄R₅; (CR₈R₈)_q C(O)NR₄R₅; (CR₈R₈)_q C(O)NR₄R₁₀; S(O)₃H; S(O)₃R₈; (CR₈R₈)_q C(O)R₁₁; C₂₋₁₀ alkenyl C(O)R₁₁; C₂₋₁₀ alkenyl C(O)OR₁₁; C(O)R₁₁; (CR₈R₈)_q C(O)OR₁₂; (CR₈R₈)_q OC(O) R₁₁; (CR₈R₈)_q NR₄C(O)R₁₁, (CR₈R₈)_q NHS(O)₂R_d, (CR₈R₈)_q S(O)₂NR₄R₅; or two Y moieties together may form O-(CH₂)_sO- or a 5 to 6 membered unsaturated ring; R₆ and R₇ are independently hydrogen or a C₁₋₄ alkyl group, or R₆ and R₇ together with the nitrogen to which they are attached form a 5 to 7 member ring which ring may optionally contain an additional heteroatom which heteroatom is selected from oxygen, nitrogen or sulfur;
- R₈ is independently selected from hydrogen or C₁₋₄ alkyl;
- R₁₀ is C₁₋₁₀ alkyl C(O)₂R₈;
- R₁₁ is hydrogen, C₁₋₄ alkyl, optionally substituted aryl, optionally substituted aryl C₁₋₄alkyl, optionally substituted heteroaryl, optionally substituted heteroarylC₁₋₄alkyl, optionally substituted heterocyclic, or optionally substituted heterocyclicC₁₋₄alkyl;
- R₁₂ is hydrogen, C₁₋₁₀ alkyl, optionally substituted aryl or optionally substituted arylalkyl;
- R₁₃ and R₁₄ are independently hydrogen or C₁₋₄ alkyl;
- R₁₇ is C₁₋₄alkyl, aryl, arylalkyl, heteroaryl, heteroarylC₁₋₄alkyl, heterocyclic, or heterocyclicC₁₋₄alkyl, wherein the aryl, heteroaryl and heterocyclic rings may all be optionally substituted;
- R_d is NR₆R₇, alkyl, arylC₁₋₄alkyl, arylC₂₋₄ alkenyl, heteroaryl, heteroaryl-C₁₋₄alkyl, heteroarylC₂₋₄ alkenyl, heterocyclic, heterocyclicC₁₋₄ alkyl, wherein the aryl, heteroaryl and heterocyclic rings may all be optionally substituted;
- E is optionally selected from



11. The compound according to Claim 10 wherein the ionizable hydrogen has a pK_a of 3 to 10.
12. The method according to Claim 10 wherein R is hydroxy, carboxylic acid, thiol, $-SR_2$, OR_2 , $NH-C(O)R_a$, $C(O)NR_6R_7$, $NHS(O)_2R_b$, $S(O)_2NHR_c$, $NHC(X_2)NHR_b$, or tetrazolyl;
- wherein R_2 is a substituted aryl, heteroaryl, or heterocyclic ring which ring contains the functional moiety providing an ionizable hydrogen having a pK_a of 10 or less;
- R_a is an alkyl, aryl, aryl C_{1-4} alkyl, heteroaryl, heteroaryl C_{1-4} alkyl, heterocyclic, or a heterocyclic C_{1-4} alkyl moiety, all of which may be optionally substituted;
- R_b is a NR_6R_7 , alkyl, aryl, aryl C_{1-4} alkyl, aryl C_{2-4} alkenyl, heteroaryl, heteroaryl C_{1-4} alkyl, heteroaryl C_{2-4} alkenyl, heterocyclic, heterocyclic C_{1-4} alkyl, heterocyclic C_{2-4} alkenyl moiety, camphor, all of which may be optionally substituted one to three times independently by halogen; nitro; halosubstituted C_{1-4} alkyl; C_{1-4} alkyl; C_{1-4} alkoxy; $NR_9C(O)R_a$; $C(O)NR_6R_7$, $S(O)_3H$, or $C(O)OC_{1-4}$ alkyl;
- R_9 is hydrogen or a C_{1-4} alkyl;
- R_c is alkyl, aryl, aryl C_{1-4} alkyl, aryl C_{2-4} alkenyl, heteroaryl, heteroaryl C_{1-4} alkyl, heteroaryl C_{2-4} alkenyl, heterocyclic, heterocyclic C_{1-4} alkyl, or a heterocyclic C_{2-4} alkenyl moiety, all of which may be optionally substituted one to three times independently by halogen, nitro, halosubstituted C_{1-4} alkyl, C_{1-4} alkyl, C_{1-4} alkoxy, $NR_9C(O)R_a$, $C(O)NR_6R_7$, $S(O)_3H$, or $C(O)OC_{1-4}$ alkyl; and

X₂ is oxygen or sulfur.

13. The compound according to Claim 12 wherein the R₂ is optionally substituted one to three times by halogen, nitro, halosubstituted C₁₋₁₀ alkyl, C₁₋₁₀ alkyl, C₁₋₁₀ alkoxy, hydroxy, SH, C(O)NR₆R₇, NH-C(O)R_a, NHS(O)₂R_b, S(O)NR₆R₇, C(O)OR₈, or a tetrazolyl ring.
14. The compound according to Claim 12 wherein R is OH, -NHS(O)₂R_b or C(O)OH.
15. The compound according to Claim 10 wherein R₁ is halogen, cyano, nitro, CF₃, C(O)NR₄R₅, alkenyl C(O)NR₄R₅, C(O)R₄R₁₀, alkenyl C(O)OR₁₂, heteroaryl, heteroarylalkyl, heteroaryl alkenyl, or S(O)NR₄R₅.
16. The compound according to Claim 10 wherein Y is hydrogen, halogen, C₁₋₄ alkoxy, optionally substituted aryl, optionally substituted arylalkoxy, or optionally substituted arylC₁₋₄alkyloxy.
17. The compound according to Claim 10 wherein R is OH, SH, or NHS(O)₂R_b and R₁ is substituted in the 3-position, the 4-position or di substituted in the 3,4-position by an electron withdrawing moiety.
18. A pharmaceutical composition comprising a compound according to any of Claims 10 to 17, and a pharmaceutically acceptable carrier or diluent.
19. A method of treating a chemokine mediated disease state, wherein the chemokine binds to an IL-8 a or b receptor in a mammal, which comprises administering to said mammal an effective amount of a compound of the formula:

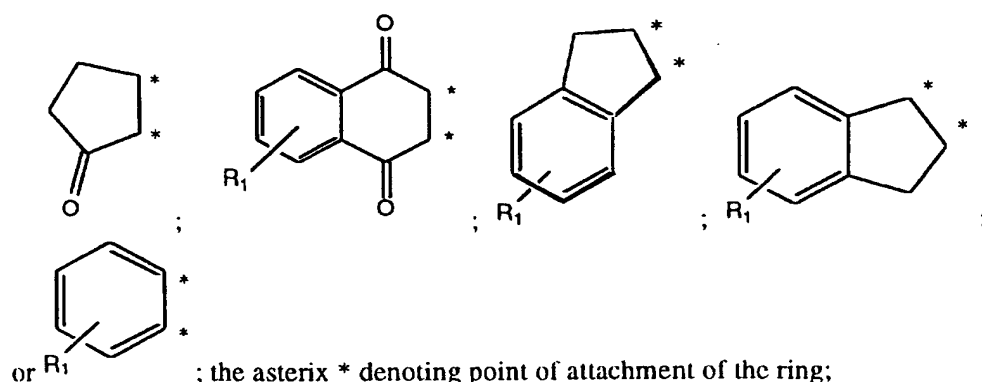


wherein

X is oxygen or sulfur;

R is any functional moiety having an ionizable hydrogen and a pKa of 10 or less;

- R₁ is independently selected from hydrogen; halogen; nitro; cyano; halosubstituted C₁₋₁₀ alkyl; C₁₋₁₀ alkyl; C₂₋₁₀ alkenyl; C₁₋₁₀ alkoxy; halosubstituted C₁₋₁₀ alkoxy; azide; (CR₈R₈)_q S(O)_tR₄; hydroxy; hydroxy C₁₋₄alkyl; aryl; aryl C₁₋₄ alkyl; aryloxy; aryl C₁₋₄ alkyloxy; heteroaryl; heteroarylalkyl; heterocyclic, heterocyclic C₁₋₄alkyl; heteroaryl C₁₋₄ alkyloxy; aryl C₂₋₁₀ alkenyl; heteroaryl C₂₋₁₀ alkenyl; heterocyclic C₂₋₁₀ alkenyl; (CR₈R₈)_qNR₄R₅; C₂₋₁₀ alkenyl C(O)NR₄R₅; (CR₈R₈)_q C(O)NR₄R₅; (CR₈R₈)_q C(O)NR₄R₁₀; S(O)₃H; S(O)₃R₈; (CR₈R₈)_q C(O)R₁₁; C₂₋₁₀ alkenyl C(O)R₁₁; C₂₋₁₀ alkenyl C(O)OR₁₁(CR₈R₈)_q C(O)OR₁₂; (CR₈R₈)_q OC(O) R₁₁; (CR₈R₈)_qNR₄C(O)R₁₁, (CR₈R₈)_q NHS(O)₂R₁₇, (CR₈R₈)_q S(O)₂NR₄R₅; or two R₁ moieties together may form O-(CH₂)_sO- or a 5 to 6 membered unsaturated ring;
- q is 0, or an integer having a value of 1 to 10;
- s is an integer having a value of 1 to 3;
- t is 0, or an integer having a value of 1 or 2;
- m is an integer having a value of 1 to 3;
- R₄ and R₅ are independently hydrogen, optionally substituted C₁₋₄ alkyl, optionally substituted aryl, optionally substituted aryl C₁₋₄alkyl, optionally substituted heteroaryl, optionally substituted heteroaryl C₁₋₄alkyl, heterocyclic, heterocyclic C₁₋₄ alkyl, or R₄ and R₅ together with the nitrogen to which they are attached form a 5 to 7 member ring which may optionally comprise an additional heteroatom selected from oxygen, nitrogen, or sulfur;
- Y is an optionally substituted C₁₋₁₀ alkyl, an optionally substituted C₂₋₁₀ alkenyl, or an optionally substituted C₂₋₁₀ alkynyl;
- R₈ is independently selected from hydrogen or C₁₋₄ alkyl;
- R₁₀ is C₁₋₁₀ alkyl C(O)₂R₈;
- R₁₁ is hydrogen, C₁₋₄ alkyl, optionally substituted aryl, optionally substituted aryl C₁₋₄alkyl, optionally substituted heteroaryl, optionally substituted heteroarylC₁₋₄alkyl, optionally substituted heterocyclic, or optionally substituted heterocyclicC₁₋₄alkyl;
- R₁₂ is hydrogen, C₁₋₁₀ alkyl, optionally substituted aryl or optionally substituted arylalkyl;
- R₁₇ is C₁₋₄alkyl, aryl, arylalkyl, heteroaryl, heteroarylC₁₋₄alkyl, heterocyclic, or heterocyclicC₁₋₄alkyl, wherein the aryl, heteroaryl and heterocyclic rings may all be optionally substituted;
- E is optionally selected from



provided that when R is OH, R_1 is 4-nitro, and E is a bond, then Y is other

- 5 than ethoxycarbonyl-2-ethyl propyl, 1-isopropyl 2- benzyloxyethyl; 2-ethoxycarbonyl ethyl, ethylisopropyl ether, 1-methyl-2-phenylbenzoxyethyl, 1-methyl-2-phenylbenzoxyethyl, 2-carboxyethyl or 1-phenyl-2-benzoxyethyl; or a pharmaceutically acceptably salt thereof.

- 10 20. The method according to Claim 19 wherein the ionizable hydrogen has a pKa of 3 to 10.

21. The method according to Claim 20 wherein R is hydroxy, carboxylic acid, thiol, SR_2 , OR_2 , $NH-C(O)R_a$, $C(O)NR_6R_7$, $NHS(O)_2R_b$, $S(O)_2NHR_c$,
15 $NHC(X_2)NHR_b$, or tetrazolyl;

wherein R_2 is a substituted aryl, heteroaryl, or heterocyclic ring which ring contains the functional moiety providing the ionizable hydrogen having a pKa of 10 or less;

- 20 R_6 and R_7 are independently hydrogen or a C₁₋₄ alkyl group, or R_6 and R_7 together with the nitrogen to which they are attached form a 5 to 7 member ring which ring may optionally contain an additional heteroatom which heteroatom is selected from oxygen, nitrogen or sulfur;

- R_a is an alkyl, aryl, aryl C₁₋₄alkyl, heteroaryl, heteroaryl C₁₋₄alkyl, heterocyclic, or a heterocyclic C₁₋₄alkyl moiety, all of which may be optionally
25 substituted;

R_b is a NR_6R_7 , alkyl, aryl, arylC₁₋₄alkyl, arylC₂₋₄alkenyl, heteroaryl, heteroarylC₁₋₄alkyl, heteroarylC₂₋₄ alkenyl, heterocyclic, heterocyclic C₁₋₄alkyl, heterocyclic C₂₋₄alkenyl moiety, camphor, all of which may be optionally

substituted one to three times independently by halogen; nitro; halosubstituted C₁₋₄ alkyl; C₁₋₄ alkyl; C₁₋₄ alkoxy; NR₉C(O)R_a; C(O)NR₆R₇, S(O)₃H, or C(O)OC₁₋₄ alkyl;

R₉ is hydrogen or a C₁₋₄ alkyl;

- 5 R_c is alkyl, aryl, arylC₁₋₄alkyl, arylC₂₋₄alkenyl, heteroaryl, heteroarylC₁₋₄alkyl, heteroarylC₂₋₄alkenyl, heterocyclic, heterocyclic C₁₋₄alkyl, or a heterocyclic C₂₋₄alkenyl moiety, all of which may be optionally substituted one to three times independently by halogen, nitro, halosubstituted C₁₋₄ alkyl, C₁₋₄ alkyl, C₁₋₄ alkoxy, NR₉C(O)R_a, C(O)NR₆R₇, S(O)₃H, or C(O)OC₁₋₄ alkyl; and
- 10 X₂ is oxygen or sulfur.

22. The method according to Claim 21 wherein the R₂ is optionally substituted one to three times by halogen, nitro, halosubstituted C₁₋₁₀ alkyl, C₁₋₁₀ alkyl, C₁₋₁₀ alkoxy, hydroxy, SH, -C(O)NR₆R₇, -NH-C(O)R_a, -NHS(O)₂R_b,
 15 S(O)NR₆R₇, C(O)OR₈, or a tetrazolyl ring.

23. The method according to Claim 21 wherein R is OH, -NHS(O)₂R_b or C(O)OH.

- 20 24. The method according to Claim 19 wherein R₁ is halogen, cyano, nitro, CF₃, C(O)NR₄R₅, alkenyl C(O)NR₄R₅, C(O)R₄R₁₀, alkenyl C(O)OR₁₂, heteroaryl, heteroarylalkyl, heteroaryl alkenyl, or S(O)NR₄R₅.

- 25 25. The method according to Claim 19 wherein Y is an optionally substituted alkyl or an optionally substituted alkenyl.

26. The method according to Claim 19 wherein R is OH, SH, or NHS(O)₂R_b and R₁ is substituted in the 3-position, the 4- position or di substituted in the 3,4- position by an electron withdrawing moiety.

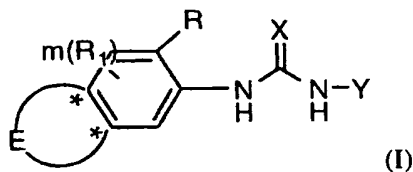
30

27. The method according to any of Claims 19 to 26 wherein the mammal is afflicted with a chemokine mediated disease selected from psoriasis, or atopic dermatitis, asthma, chronic obstructive pulmonary disease, adult respiratory distress syndrome, arthritis, inflammatory bowel disease, Crohn's disease, ulcerative colitis,
 35 septic shock, endotoxic shock, gram negative sepsis, toxic shock syndrome, stroke,

cardiac and renal reperfusion injury, glomerulo-nephritis, thrombosis, neurotrauma, alzheimers disease, graft vs. host reaction, or allograft rejections.

28. A compound of the formula:

5



wherein

X is oxygen or sulfur;

R is any functional moiety having an ionizable hydrogen and a pKa of 10 or less;

10 R₁ is independently selected from hydrogen; halogen; nitro; cyano; halosubstituted C₁₋₁₀ alkyl; C₁₋₁₀ alkyl; C₂₋₁₀ alkenyl; C₁₋₁₀ alkoxy; halosubstituted C₁₋₁₀ alkoxy; azide; (CR₈R₈)_q S(O)_tR₄; hydroxy; hydroxy C₁₋₄alkyl; aryl; aryl C₁₋₄ alkyl; aryloxy; aryl C₁₋₄ alkyloxy; heteroaryl; heteroarylalkyl; heterocyclic, heterocyclic C₁₋₄alkyl; heteroaryl C₁₋₄ alkyloxy; aryl C₂₋₁₀ alkenyl; heteroaryl C₂₋₁₀ alkenyl; heterocyclic C₂₋₁₀ alkenyl; (CR₈R₈)_qNR₄R₅; C₂₋₁₀ alkenyl C(O)NR₄R₅; (CR₈R₈)_q C(O)NR₄R₅; (CR₈R₈)_q C(O)NR₄R₁₀; S(O)₃H; S(O)₃R₈; (CR₈R₈)_q C(O)R₁₁; C₂₋₁₀ alkenyl C(O)R₁₁; C₂₋₁₀ alkenyl C(O)OR₁₁(CR₈R₈)_q C(O)OR₁₂; (CR₈R₈)_q OC(O) R₁₁; (CR₈R₈)_qNR₄C(O)R₁₁, (CR₈R₈)_q NHS(O)₂R₁₇, (CR₈R₈)_q S(O)₂NR₄R₅; or
20 two R₁ moieties together may form O-(CH₂)_sO- or a 5 to 6 membered unsaturated ring;

q is 0, or an integer having a value of 1 to 10;

s is an integer having a value of 1 to 3;

t is 0, or an integer having a value of 1 or 2;

25 m is an integer having a value of 1 to 3;

R₄ and R₅ are independently hydrogen, optionally substituted C₁₋₄ alkyl, optionally substituted aryl, optionally substituted aryl C₁₋₄alkyl, optionally substituted heteroaryl, optionally substituted heteroaryl C₁₋₄alkyl, heterocyclic, heterocyclic C₁₋₄ alkyl, or R₄ and R₅ together with the nitrogen to which they
30 are attached form a 5 to 7 member ring which may optionally comprise an additional heteroatom selected from oxygen, nitrogen, or sulfur;

Y is an optionally substituted C₁₋₁₀ alkyl, an optionally substituted C₂₋₁₀ alkenyl, or an optionally substituted C₂₋₁₀ alkynyl;

R₈ is independently selected from hydrogen or C₁₋₄ alkyl;

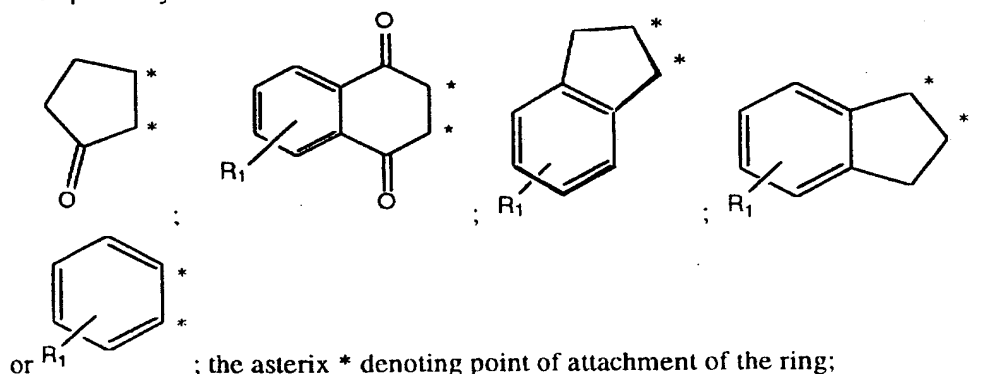
R₁₀ is C₁₋₁₀ alkyl C(O)₂R₈;

R₁₁ is hydrogen, C₁₋₄ alkyl, optionally substituted aryl, optionally substituted aryl C₁₋₄alkyl, optionally substituted heteroaryl, optionally substituted heteroarylC₁₋₄alkyl, optionally substituted heterocyclic, or optionally substituted heterocyclicC₁₋₄alkyl;

R₁₂ is hydrogen, C₁₋₁₀ alkyl, optionally substituted aryl or optionally substituted arylalkyl;

R₁₇ is C₁₋₄alkyl, aryl, arylalkyl, heteroaryl, heteroarylC₁₋₄alkyl, heterocyclic, or heterocyclicC₁₋₄alkyl, wherein the aryl, heteroaryl and heterocyclic rings may all be optionally substituted;

E is optionally selected from



provided that when R is OH, R₁ is 4-nitro, and E is a bond, then Y is other than ethoxycarbonyl-2-ethyl propyl, 1-isopropyl 2- benzyloxyethyl; 2-ethoxycarbonyl ethyl, ethylisopropyl ether, 1-methyl-2-phenylbenzoxymethyl, 1-methyl-2-phenylbenzoxymethyl, 2-carboxyethyl or 1-phenyl-2-benzoxymethyl; or a pharmaceutically acceptably salt thereof.

29. The compound according to Claim 28 wherein the ionizable hydrogen has a pK_a of 3 to 10.

30. The method according to Claim 28 wherein R is hydroxy, carboxylic acid, thiol, SR₂, OR₂, NH-C(O)R_a, C(O)NR₆R₇, NHS(O)₂R_b, S(O)₂NHR_c, NHC(X₂)NHR_b, or tetrazolyl;

wherein R₂ is a substituted aryl, heteroaryl, or heterocyclic ring which ring contains the functional moiety providing an ionizable hydrogen having a pK_a of 10 or less;

R₆ and R₇ are independently hydrogen or a C₁₋₄ alkyl group, or R₆ and R₇ together with the nitrogen to which they are attached form a 5 to 7 member ring which ring may optionally contain an additional heteroatom which heteroatom is selected from oxygen, nitrogen or sulfur;

R_a is an alkyl, aryl, aryl C₁₋₄alkyl, heteroaryl, heteroaryl C₁₋₄alkyl, heterocyclic, or a heterocyclic C₁₋₄alkyl moiety, all of which may be optionally substituted;

R_b is a NR₆R₇, alkyl, aryl, arylC₁₋₄alkyl, arylC₂₋₄alkenyl, heteroaryl, heteroarylC₁₋₄alkyl, heteroarylC₂₋₄alkenyl, heterocyclic, heterocyclic C₁₋₄alkyl, heterocyclic C₂₋₄alkenyl moiety, camphor, all of which may be optionally substituted one to three times independently by halogen; nitro; halosubstituted C₁₋₄alkyl; C₁₋₄alkyl; C₁₋₄alkoxy; NR₉C(O)R_a; C(O)NR₆R₇, S(O)₃H, or C(O)OC₁₋₄alkyl;

R₉ is hydrogen or a C₁₋₄alkyl;

R_c is alkyl, aryl, arylC₁₋₄alkyl, arylC₂₋₄alkenyl, heteroaryl, heteroarylC₁₋₄alkyl, heteroarylC₂₋₄alkenyl, heterocyclic, heterocyclic C₁₋₄alkyl, or a heterocyclic C₂₋₄alkenyl moiety, all of which may be optionally substituted one to three times independently by halogen, nitro, halosubstituted C₁₋₄alkyl, C₁₋₄alkyl, C₁₋₄alkoxy, NR₉C(O)R_a, C(O)NR₆R₇, S(O)₃H, or C(O)OC₁₋₄alkyl; and X₂ is oxygen or sulfur.

31. The compound according to Claim 28 wherein the R₂ is optionally substituted one to three times by halogen, nitro, halosubstituted C₁₋₁₀alkyl, C₁₋₁₀alkyl, C₁₋₁₀alkoxy, hydroxy, SH, C(O)NR₆R₇, NH-C(O)R_a, NHS(O)₂R_b, S(O)NR₆R₇, C(O)OR₈, or a tetrazolyl ring.

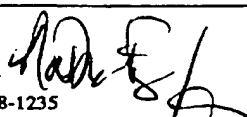
32. The compound according to Claim 28 wherein R is OH, -NHS(O)₂R_b or C(O)OH.

33. The compound according to Claim 28 wherein R₁ is halogen, cyano, nitro, CF₃, C(O)NR₄R₅, alkenyl C(O)NR₄R₅, C(O)R₄R₁₀, alkenyl C(O)OR₁₂, heteroaryl, heteroarylalkyl, heteroaryl alkenyl, or S(O)NR₄R₅.

34. The compound according to Claim 28 wherein Y is optionally substituted alkyl or is an optionally substituted alkenyl.
35. The compound according to Claim 28 wherein R is OH, SH, or NHS(O)₂R_b and R₁ is substituted in the 3-position, the 4- position or di substituted in the 3,4-position by an electron withdrawing moiety.
36. The compound according to Claim 28 which is:
 N-Allyl-N'-(2-hydroxy-4-nitrophenyl)urea
 10 N-t-Butyl-N'-(2-hydroxy-4-nitrophenyl)urea
 N-[2-(Ethoxycarbonyl)propyl]-N'-(2-hydroxy-4-nitrophenyl)urea
 N-Isopropyl-N'-(2-hydroxy-4-nitrophenyl)urea
 N-(1-(Ethoxycarbonyl)ethyl)-N'-(2-hydroxy-4-nitrophenyl)urea
 N-(Dimethylacetal)-N'-(2-hydroxy-4-nitrophenyl)urea
 15 N-(2-Methoxyethyl)-N'-(2-hydroxy-4-nitrophenyl)urea
 N-(2-Benzoyloxypropyl)-N'-(2-hydroxy-4-nitrophenyl)urea
 N-(2-methoxyisopropyl)-N'-(2-hydroxy-4-nitrophenyl)urea
 N-(1-carbonyl-2-methylpropyl)-N'-(2-hydroxy-4-nitrophenyl)urea
 N-(1,1-Dimethyl-2-benzoyloxyethyl)-N'-(2-hydroxy-4-nitrophenyl)urea
 20 N-(1,2-dimethyl-2-benzoyloxyethyl)-N'-(2-hydroxy-4-nitrophenyl)urea
 N-(2-benzenesulfonylamino-4-cyanophenyl)-N'-(isopropyl)urea
 N-(2-Hydroxy-4-nitrophenyl)-N'-(2-methoxyethyl)urea
 N-(2-Hydroxy-4-nitrophenyl)-N'-(2-benzoyloxypropyl)urea
 N-(2-Hydroxy-4-nitrophenyl)-N'-(2-methoxyisopropyl)urea
 25 N-(2-Hydroxy-4-nitrophenyl)-N'-(1-carbonyl-2-methylpropyl)urea
 N-(2-Hydroxy-4-nitrophenyl)-N'-(1,2-dimethyl-2-benzoyloxyethyl)urea
 N-(2-Benzenesulfonylamino-4-cyanophenyl)-N'-(isopropyl)ure;
 or pharmaceutically acceptable salts thereof.
- 30 37. A pharmaceutical composition comprising a compound according to any of Claims 28 to 36, and a pharmaceutically acceptable carrier or diluent.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US97/10903

A. CLASSIFICATION OF SUBJECT MATTER IPC(6) : C07C 335/00, 273/00 US CL : 514/585-587, 596-598; 564/17, 30-32, 47-53, 57 According to International Patent Classification (IPC) or to both national classification and IPC																				
B. FIELDS SEARCHED Minimum documentation searched (classification system followed by classification symbols) U.S. : 514/585-587, 596-598; 564/17, 30-32, 47-53, 57 Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched Electronic data base consulted during the international search (name of data base and, where practicable, search terms used) APS, CAS ONLINE, REGISTRY, WPIDS																				
C. DOCUMENTS CONSIDERED TO BE RELEVANT																				
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.																		
X	US 5,106,873 A (O'BRIEN et al) 21 April 1992, see columns 1-5.	10, 11, 13-18, 28-35, 37																		
X, P	US 5,621,010 A (SUEDA et al) 15 April 1997, see Example 15.	10, 11, 13-18, 28-31, 33, 34, 37																		
X, P	US 5,585,518 A (MARSCHNER et al) 17 December 1996, see Examples 1, 3, 6, and 7.	28-36																		
A	HOWARD, O.M.Z. et al. Chemokines: Progress toward Identifying Molecular Targets for Therapeutic Agents. TIBTECH. February 1996, Vol. 14, pages 46-51.	1-37																		
<input type="checkbox"/> Further documents are listed in the continuation of Box C. <input type="checkbox"/> See patent family annex.																				
<table border="0"><tr><td colspan="2">* Special categories of cited documents:</td><td>*T* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention</td></tr><tr><td>*A*</td><td>document defining the general state of the art which is not considered to be of particular relevance</td><td></td></tr><tr><td>*B*</td><td>earlier document published on or after the international filing date</td><td>*X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone</td></tr><tr><td>*L*</td><td>document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)</td><td>*Y* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art</td></tr><tr><td>*O*</td><td>document referring to an oral disclosure, use, exhibition or other means</td><td></td></tr><tr><td>*P*</td><td>document published prior to the international filing date but later than the priority date claimed</td><td>*A* document member of the same patent family</td></tr></table>			* Special categories of cited documents:		*T* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention	*A*	document defining the general state of the art which is not considered to be of particular relevance		*B*	earlier document published on or after the international filing date	*X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone	*L*	document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	*Y* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art	*O*	document referring to an oral disclosure, use, exhibition or other means		*P*	document published prior to the international filing date but later than the priority date claimed	*A* document member of the same patent family
* Special categories of cited documents:		*T* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention																		
A	document defining the general state of the art which is not considered to be of particular relevance																			
B	earlier document published on or after the international filing date	*X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone																		
L	document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	*Y* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art																		
O	document referring to an oral disclosure, use, exhibition or other means																			
P	document published prior to the international filing date but later than the priority date claimed	*A* document member of the same patent family																		
Date of the actual completion of the international search 16 SEPTEMBER 1997		Date of mailing of the international search report 30 OCT 1997																		
Name and mailing address of the ISA/US Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231 Facsimile No. (703) 305-3230		Authorized officer GARTH M. DAHLEN  Telephone No. (703) 308-1235																		

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US97/10903

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

Please See Extra Sheet.

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:
1-37 (in part)

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US97/10903**BOX II. OBSERVATIONS WHERE UNITY OF INVENTION WAS LACKING**

This ISA found multiple inventions as follows:

This application contains the following inventions or groups of inventions which are not so linked as to form a single inventive concept under PCT Rule 13.1. In order for all inventions to be searched, the appropriate additional search fees must be paid.

Group I, claims 1-37 (in part), drawn to compounds where the variable Y in claims 1-18 is limited to the instantly claimed radicals that have either an -O-, -S-, or -N- bonded directly to the cycloalkyl group, and the variable Y in claims 19-37 is limited to a mono-substituted alkyl group wherein the substitution occurs through either an -O-, -S-, or -N- and the phenyl ring bonded to the variable R is not further condensed so as to form a polycyclo, compositions, and methods of use.

Group II, claims 1-37 (in part), drawn to the instant compounds not encompassed by Group I, compositions, and methods of use.

The inventions listed as Groups I and II do not relate to a single inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, they lack the same or corresponding special technical features for the following reasons: The claims are drawn to alternative products not having a corresponding technical feature, i.e., the common N-C-N group is not deemed a substantial core. The requirement of a technical interrelationship and the same or corresponding special technical features shall be considered to be met when the alternatives are of a similar nature where the following criteria are fulfilled:

- (A) all alternatives have a common property or activity, and
- (B)(1) a common structure is present, i.e., a significant structural element is shared by all of the alternatives, or
- (B)(2) in cases where the common structure cannot be the unifying criteria, all alternatives belong to a recognized class of chemical compounds in the art to which the invention pertains.

In section (B)(1), above, the phrase "significant structural element is shared by all of the alternatives" refers to cases where the compounds share a common chemical structure which occupies a large portion of their structures, or in case the compounds have in common only a small portion of their structures, the commonly shared structure constitutes a structurally distinctive portion in view of existing prior art. The structural element may be a single component or a combination of individual components linked together.

The examiner maintains that the requirement of (B)(1) has not been met since the structural element common to all of the alternatives, i.e., N-C-N, constitutes too small portion of the compound's structure to be considered structurally distinctive.

During a telephone conversation on September 15, 1997, Applicant's Attorney Ms. Dara L. Dinner elected not to pay the search fees for Group II.